The American Journal of Medicine

December 1955

The American Journal of Medicine

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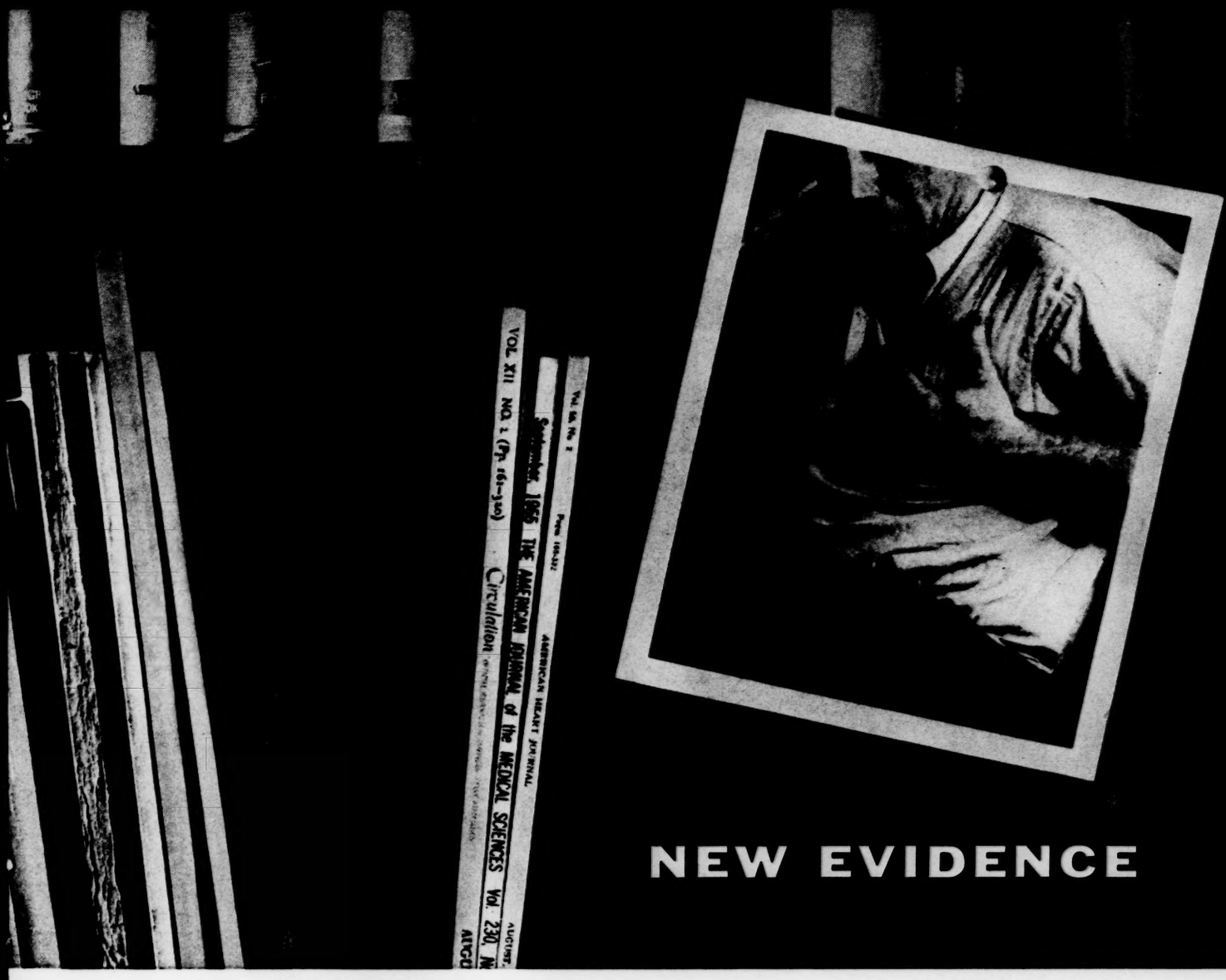

How you can prevent attacks of angina pectoris

Three new studies have recently been added to the extensive investigation of Peritrate's effectiveness in preventing attacks of angina pectoris:

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"Impressive and sustained improvement" was also observed in a small number of patients treated by Kory *et al. Am. Heart J.* 50:*308 (Aug.) 1955.*

Among anginal prophylactic drugs evaluated by Russek's group "only this agent [Peritrate] appears worthy of the designation, 'long-acting coronary vasodilator.'" *Circulation* 12:*169 (Aug.) 1955.*

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The American Journal of Medicine

Vol. XIX DECEMBER, 1955 No. 6

Editorial

Clinical Studies

In a study of unusual interest, Dr. Prinzmetal and his associates used ingeniously devised needle electrodes to obtain, in twelve patients undergoing thoracotomy, direct intramural electrocardiographic records of the activation of the human ventricle. The results conflict in some essentials with classic theory but are in accord with previous observations by this group in similar studies on the dog and with conclusions reached by other investigators. The positive component of the depolarization complex was found wholly or in large part to be generated in the outer layers of the myocardium, the subendocardium being electrocardiographically silent in this respect, in part perhaps because of the very rapid rate of impulse transmission there. Similar differences between the inner and outer layers of the myocardium were found also in respect to generation of injury potentials, as reflected in displacement of the S-T segment. The implications as to interpretation of clinical electrocardiograms, especially in connection with subendocardial infarction, are apparent, and many other points of interest are made.

The development of phonocardiography, and particularly of the more precise spectral phonocardiography, has made it possible to subject the auscultatory phenomena of the normal and disordered heart to more exact analysis. The results are of great interest and clinical value, as exemplified by the present study of the much confused phenomenon of splitting of heart sounds. The article deserves careful study because it clarifies many clinical obscurities of daily practice. For example, it explains why P-2 occasionally is louder than A-2 in systemic arterial hypertension; the influence of respiration on splitting of the second sound; the significance of splitting in interatrial septal defects, left and right bundle branch block, valvular defects, various respiratory tract disorders, and many other points of interest.

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CORTROPHIN-ZINC

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- ACTION LASTS AT LEAST 24 TO 72 HOURS
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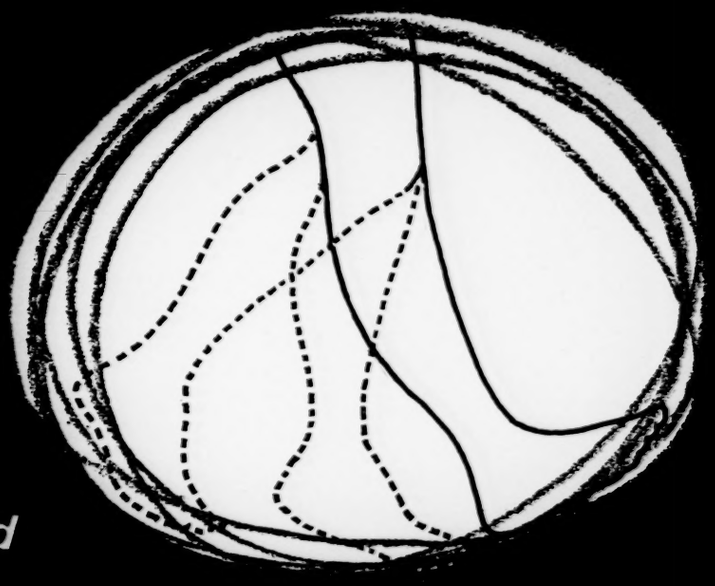

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1. Forsham, P. H., et al.: Paper presented at First Internat. Conf. on Prednisone and Prednisolone, New York, N. Y., May 31-June 1, 1955

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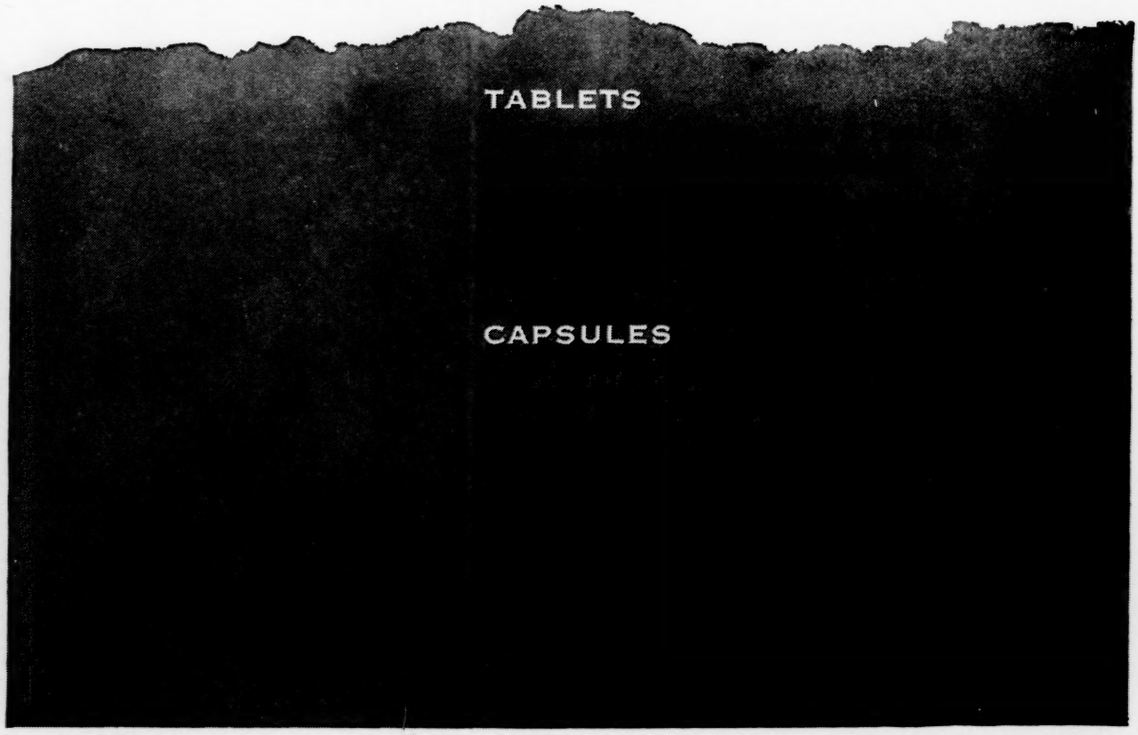

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1. Eisenberg, et al., Antib. & Chemo., 3:1026-1028, Oct., 1953.

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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954. 2. Sebrell, W.H., Jr.: J.A.M.A. 152:42 (May) 1953. 3. Sherman, R.J.: Medical Times, 82:107 (Feb.) 1954.

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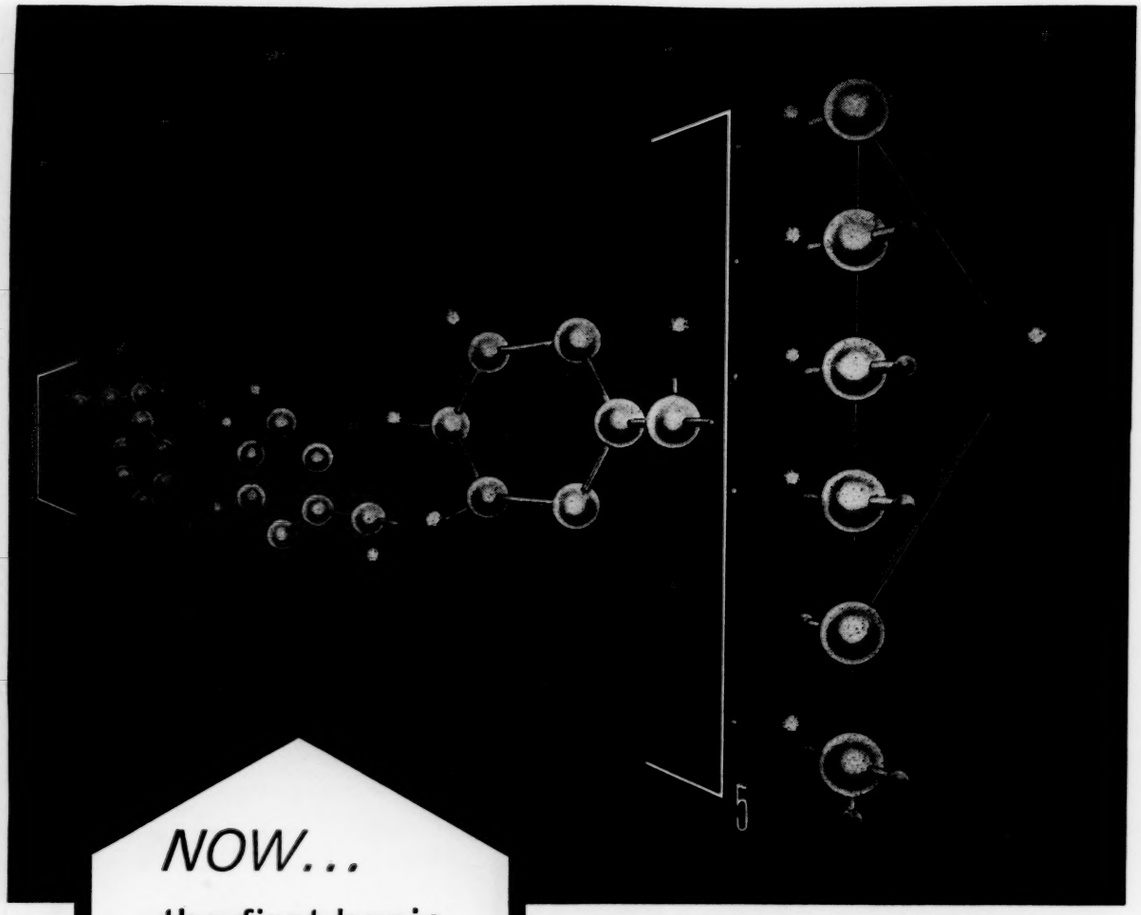

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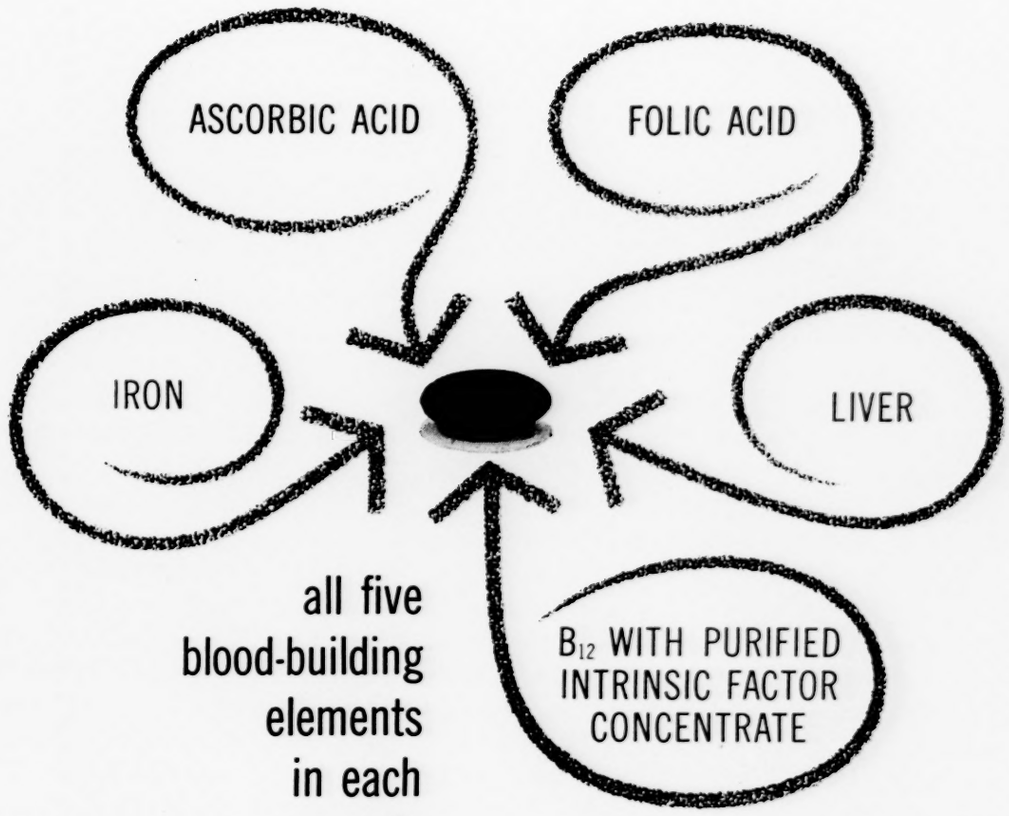

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1. Shackman, N. H.: Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct.) 1954. • 2. Stollerman, G. H., and others: Am. J. Med. 15:645 (Nov.) 1953. • 3. McEwen, C.: M. Clin. North America 39:353 (March) 1955. • 4. Wood, H. F., and McCarty, M.: Am. J. Med. 17:768 (Dec.) 1954. • 5. McEwen, C., and Ziff, M.: M. Clin. North America (May) 1955, to be published.

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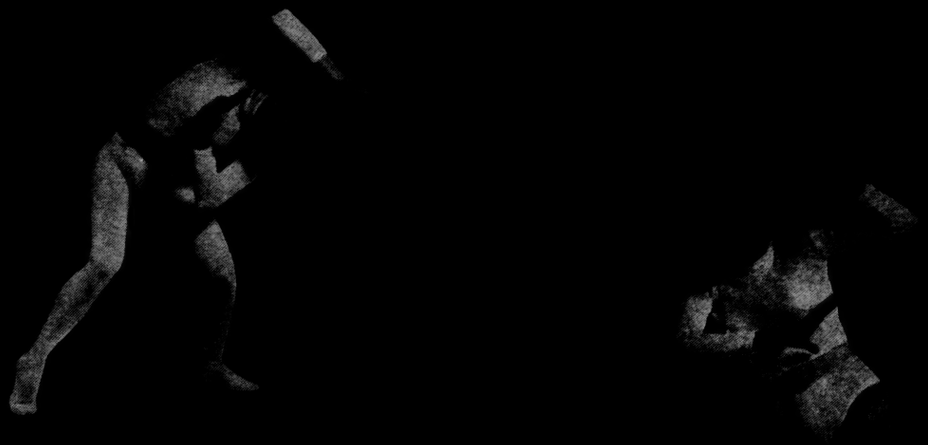

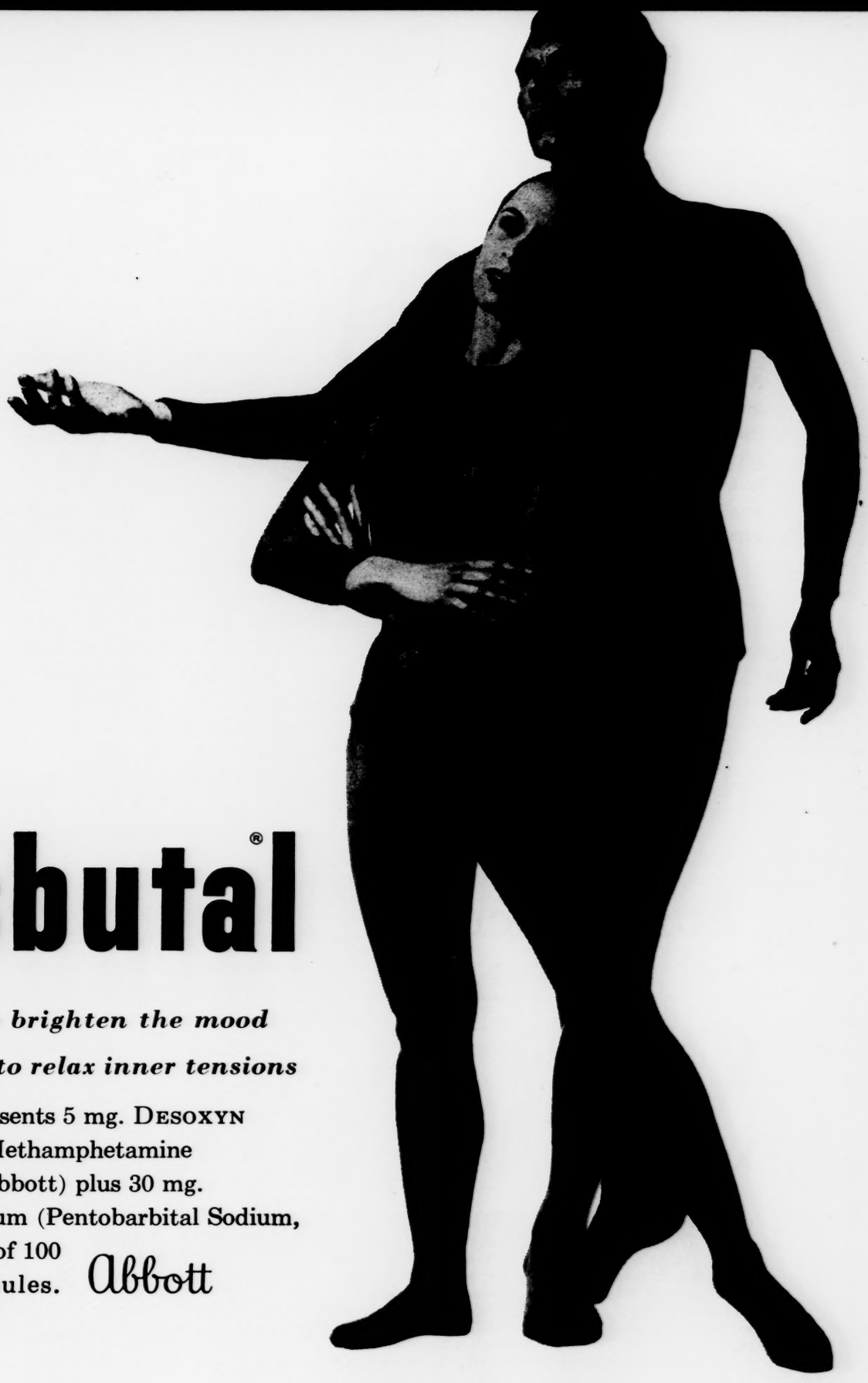

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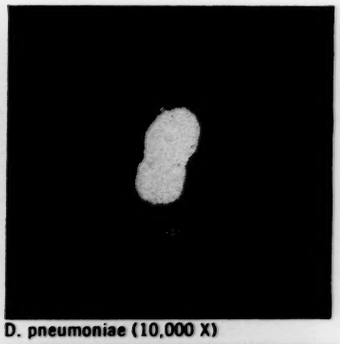
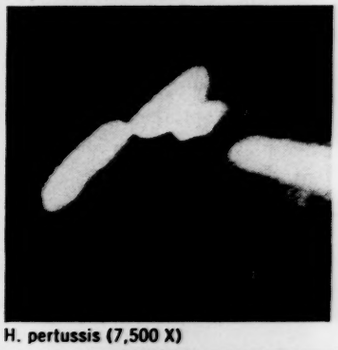
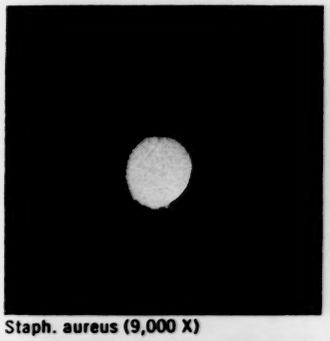


D. pneumoniae (10,000 X)

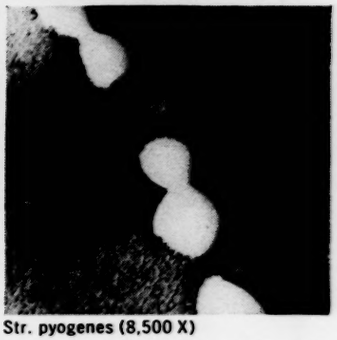
K. pneumoniae (13,000 X)



H. pertussis (7,500 X)



Staph. aureus (9,000 X)



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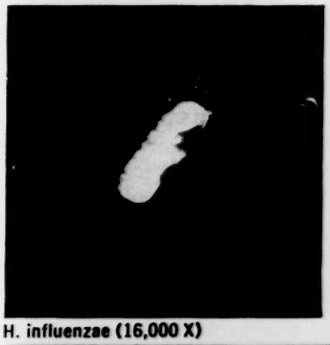

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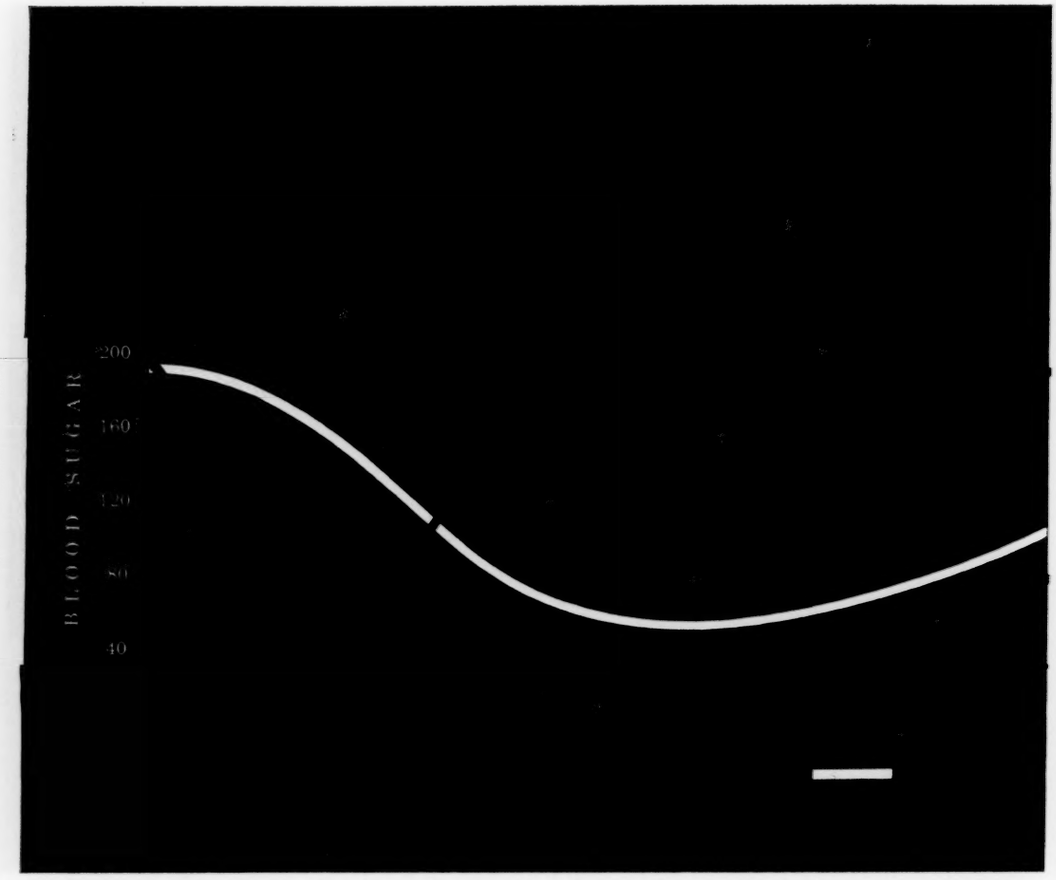

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The American Journal of Medicine

VOL. XIX DECEMBER, 1955 NO. 6

Editorial

Pathergic Granulomatosis

THE peculiar tissue changes involving particularly the respiratory tract, kidneys and spleen which were first described by Klinger[1] in 1931 and later by Wegener[2] in 1936 have been called Wegener's granulomatosis or syndrome. Other terms applied to this syndrome include necrotizing granulomatosis and angiitis, respiratory-renal type of polyarteritis nodosa, atypical periarteritis nodosa, giant cell granuloma, granuloma with periarteritis nodosa, rhinogenous granuloma (Wegener's original term), rheumatic vascular inflammation, pararheumatic disorder, Loeffler's syndrome and hemorrhagic and interstitial pneumonitis with nephritis. Recently, because of the appearance of these lesions in asthmatics and of the histologic characteristics found, Ehrlich and Romanoff[3] and Churg and Strauss[4] have called this entity allergic granulomatosis. It is the consensus of most contemporary observers of this disease that a sensitivity phenomenon is involved but the term allergic granulomatosis appears inappropriate since the disease may occur without asthma, and a less restricted term seems necessary. Fahey et al.[5] have complicated the question of nomenclature still further by attempting to separate cases of allergic granuloma from what they designate Wegener's granulomatosis with a predominance of necrotizing granulomatous lesions in the respiratory tract and the usual absence of clinical stigmata of allergy or tissue eosinophilia. Yet they noted one case which had the features of Wegener's granulomatosis together with a history of allergy and tissue eosinophilia. Furthermore, they admit the close histologic similarity between the cases of allergic granulomatosis and Wegener's granulomatosis. Ahlström, Liedholm and Truedsson[6] divide their cases into severe and mild nasopharyngeal types but believe that they are essentially the same.

It can hardly be doubted that this plethora of terms has added to the confusion regarding this disease. Consequently, the writer began a search through the literature in an attempt to devise a term which would be more satisfactory, particularly from the aspect of pathogenesis. During this search, Rössle's definition[7] of pathergy as the totality of the morbid phenomena which can be produced by a state of altered reactivity was noted. This definition fits nicely the prevailing concept of pathogenesis of this type of granulomatosis so the term pathergic granulomatosis was chosen and is offered as most suitable for the complex disease under discussion.

It is proposed that pathergic granulomatosis be divided into two varieties. The first is disseminated pathergic granulomatosis which may be viewed as the total possible expression of the

[1] KLINGER, H. Grenzformen der Periarteritis nodosa. *Frankfurt. Ztschr. f. Path.*, 42: 455, 1931.

[2] WEGENER, F. Über generalisierte, septische Gefässerkrankungen. *Verhandl. d. deutsch. path. Gesellsch.*, 29: 202, 1936; Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arterien-systems und der Nieren. *Beitr. z. path. Anat. u. z. allg. Path.*, 102: 36, 1939.

[3] EHRLICH, J. C. and ROMANOFF, A. Allergic granuloma of the lung, clinical and anatomic findings in a patient with bronchial asthma and eosinophilia. *Arch. Int. Med.*, 87: 259, 1951.

[4] CHURG, J. and STRAUSS, L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. *Am. J. Path.*, 27: 277, 1951.

[5] FAHEY, J. L., LEONARD E., CHURG, J. and GODMAN, G. Wegener's granulomatosis. *Am. J. Med.*, 17: 168, 1954.

[6] AHLSTRÖM, C. G., LIEDHOLM, K. and TRUEDSSON, E. Respirato-renal type of polyarteritis nodosa. *Acta med. Scandinav.*, 144: 323, 1953.

[7] RÖSSLE, R. Allergie und Pathergie. *Klin. Wchnschr.*, 12: 574, 1933.

pathergic process, with many organs and tissues involved; the second variety, in which only a single organ or a portion of an organ is involved without progression to the disseminated form, is designated focal pathergic granulomatosis.

In disseminated pathergic granulomatosis,[8] cough, weakness, fever, night sweats and hemoptysis may continue for years or a fatal termination may occur within a month. In some cases asthma may precede the development of granulomatosis. Abnormal respiratory signs are observed unilaterally or bilaterally on physical examination. In the roentgenogram, single circumscribed opacities may be visible; they may be mistaken for tumor or abscess. Subsequently, multiple lesions of the lungs appear as the disease progresses, and these are accompanied by signs of involvement of the kidney such as urinary albumin, casts, red cells and even gross hematuria. Finally, uremia supervenes. In other cases a diffuse, bilateral process in the lungs visible in the roentgenogram as a confluent, miliary type of infiltration is accompanied by involvement of the kidney at the onset of the disease. Other clinical manifestations noted in these cases have included bloody rectal discharge, epistaxis, marked conjunctivitis, photophobia, petechiae of the skin and ulcerations of the skin and mucous membranes. The blood eosinophilia which has been noted in these cases is often evanescent and disappears in the acute or terminal phases of the disease.

Examination of the lungs grossly in cases of disseminated pathergic granulomatosis reveals single or multiple firm, well circumscribed masses in some cases and more diffuse lesions in others. Granulomatous lesions are found microscopically, with marked ulceration and occlusion of the bronchi and bronchioles, fibroblastic proliferation, focal necroses with palisaded cells, numerous vacuolated macrophages, giant multinucleated cells, and inflammation and necrosis of arteries and veins. In surgically removed pulmonary lesions, eosinophils are found but these are usually absent in postmortem tissues in which superimposed diffuse necrosis of the granulomatous lesions is striking. Massive or spotty necrosis of the spleen and thrombotic granulomatous glomerulonephritis, in which granulomata, glomerular thrombi, crescents and angiitis are present, are commonly seen at autopsy. In some but not all cases extensive destruction of the nose and accessory sinuses may be observed. Ulcerations of the oral mucous membranes, trachea, skin, gastrointestinal tract and bladder and focal necroses of the lymph nodes may occur. While lesions similar to those found in periarteritis nodosa have been observed in regions such as the gastrointestinal tract, they may be absent.

Bacteriologic studies of lesions of the lungs and other organs give either negative results or yield bacteria which are secondary invaders.

An example of focal pathergic granulomatosis[9] is found in idiopneumonic pathergic granulomatosis. Hemoptysis, unilateral chest pain, night sweats, shortness of breath, wheezing, coughing and fatigue accompanied by unilateral rhonchi and rales occur in this entity. In the roentgenogram, unilateral fairly well demarcated patches of consolidation may be seen in the lungs. The lesions are composed of granulomatous tissue with extensive collagenization and remnants of elastic layers of blood vessels present. Ulceration and occlusion of the small bronchi and bronchioles, as in the disseminated form, may be seen as well as numerous vacuolated macrophages in the parenchyma peripheral to the involved portion of the bronchial tree.

Another possible example of a more restricted type of involvement is seen in pneumonitis of the cholesterol type.[9] Here non-bacterial mucosal ulceration and obstruction of the smaller branches of the bronchial tree due to a hypersensitivity reaction of the Arthus type is held responsible for the massive accumulations of lipoid-filled phagocytes and the fibrosis in the adjacent parenchyma of the lung. These changes are identical with the pneumonitis found peripheral to obstruction of a bronchus by a tumor. Clinically, pneumonitis of the cholesterol type is marked by cough, chills, fever, sweating, anorexia, fatigue, malaise, loss of weight, elevated temperature, hemoptysis, dyspnea, sharp to dull chest pain and cough productive of sputum. Some of these signs may be caused by secondary infection of the obstructed bronchi and bronchioles. In the roentgenogram the lesions of pneumonitis of the cholesterol type vary. Collapsed lobes, opaque masses, nodulation and cavitation may be seen. Surgical resection of

[8] FIENBERG, R. Necrotizing granulomatosis and angiitis of the lungs with massive splenic necrosis and focal thrombotic granulomatous glomerulonephritis. *Am. J. Clin. Path.*, 23: 413, 1953.

[9] FIENBERG, R. Necrotizing granulomatosis and angiitis of the lungs and its relationship to chronic pneumonitis of the cholesterol type. *Am. J. Path.*, 29: 913, 1953.

the involved portions of the lung has proved beneficial.

The question as to whether or not certain cases of so-called eosinophilic granuloma of the lung may be included as focal types of pathergic granulomatosis is difficult to answer. Numerous eosinophils may be found in pulmonary lesions of the disseminated form, thus creating the impression of an eosinophilic granuloma. It should be noted that pulmonary lesions similar to those found in disseminated pathergic granulomatosis accompanied by eosinophilia have been called Loeffler's syndrome by von Meyenburg[10] and Bayley et al.,[11] among others.

Another interesting syndrome which may be interpreted as a focal manifestation of pathergic granulomatosis is Cogan's syndrome[12] in which non-syphilitic interstitial keratitis and bilateral deafness are found. Eosinophilia has been observed in some of these cases. Evidence that these cases may be linked with pathergic granulomatosis may be found in the report by Oliver et al.[13] in which subcutaneous granulomatous nodules and angiitis were detected in a patient with Cogan's syndrome. Certainly the published illustrations of the subcutaneous nodules are reminiscent of pathergic granulomatosis.

In the literature pathergic granulomatosis has often been linked with periarteritis nodosa and has been thought of as a borderline type or as true periarteritis nodosa with added granulomatous lesions. The belief has grown that granulomatous lesions are caused by arterial changes but the absence of granulomatous lesions and of phlebitis in cases of extensive arterial lesions in periarteritis nodosa as well as the absence of arterial changes in some cases of disseminated pathergic granulomatosis has been glossed over. Another interpretation may be offered, however, in which the arterial system would be considered a single organ and limitation of the involvement to the arteries would constitute a form of focal pathergic granulomatosis. Thus the arterial lesions in periarteritis nodosa would not lead *per se* to extravascular granulomatous lesions but, in those cases in which lesions of arteries characteristic of periarteritis are present together with extravascular granulomatous lesions, either might be considered a result of the pathergic process and neither would be dependent on the other for its pathogenesis.

ROBERT FIENBERG, M.D.
Beverly Hospital,
Beverly, Massachusetts

[10] VON MEYENBURG, H. Das eosinophile Lungeninfiltrat; pathologische Anatomie und Pathogenese. *Schweiz. med. Wchnschr.*, 72: 809, 1942.

[11] BAYLEY, E. C., LINDBERG, D. O. N. and BAGENSTOSS, A. H. Loeffler's syndrome; report of a case with pathologic examination of the lungs. *Arch. Path.*, 40: 376, 1945.

[12] COGAN, D. G. Syndrome of nonsyphilitic interstitial keratitis with vestibuloauditory symptoms. *Arch. Ophth.*, 33: 144, 1945; Ibid, 42: 42, 1949.

[13] OLIVER, L., TAUBENHAUS, M., SHAPIRA, T. M. and LESHIN, N. Nonsyphilitic interstitial keratitis and bilateral deafness (Cogan's syndrome) associated with essential polyangitis (periarteritis nodosa) *New England J. Med.*, 248: 1001, 1953.

Clinical Studies

Studies on the Mechanism of Ventricular Activity*

XVI. Activation of the Human Ventricle

RASHID A. MASSUMI, M.D.,† ALFRED GOLDMAN, M.D., LOUIS RAKITA, M.D.,‡
Los Angeles, California *Duarte, California* *Cleveland, Ohio*
KIYOSHI KURAMOTO, M.D. *and* MYRON PRINZMETAL, M.D.
Los Angeles, California

THE classic theory of the mechanism of activation of the mammalian ventricular wall evolved from the pioneer work of Lewis and Rothschild in 1915[1] and subsequent observations made by a number of other investigators. In these studies the mode of depolarization of the myocardial wall from endocardium to epicardium was inferred by the study of the electrical potentials in the cavity of the ventricles on the one hand and on the epicardial surface on the other. Electrocardiographic properties of the intramural layers situated between endocardium and epicardium were not studied until recent years.

Activation of the ventricular wall, according to classic theory which is based on animal experimentation, is accomplished by advance of the activation front, at a constant rate, from endocardium to epicardium. All layers of the myocardium are assumed to contribute in proportion to their thickness to the genesis of electrocardiographic deflections. For instance, the R wave of the depolarization complex is said to begin in the endocardium and increase progressively in amplitude as the activation front approaches the epicardium. The S wave is supposed to decrease in amplitude from endocardium to epicardium. This theory was applied to human electrocardiography and has since served as the basis for interpretation of both normal and pathologic electrocardiographic deflections.

Attempts at direct electrocardiographic studies of the human heart were made as early as 1929 when Barker and his associates obtained records by placing electrodes directly on the surface of a heart exposed following pericardiostomy.[2] In 1942 Nylin and Crafoord[3] obtained direct electrocardiograms in two patients subjected to thoracotomy for pneumonectomy. Groedel and Borchardt[4] studied direct electrocardiography in 100 patients with pneumothorax and other affections of the lungs.

The development of the technic of cardiac catheterization made it possible to record potentials from the human cardiac cavities. Thus Lenègre and Maurice,[5] Hecht,[6] Sodi-Pallares and his co-workers,[7] Kisch et al.,[8] Duchosal and associates,[9] Kert and Hoobler,[10] Kossman and co-workers,[11] Wenger et al.,[12] Levine and his associates,[13–15] and others studied potential variations of right intracardiac and intravascular cavities. More recently, Seligman and his associates,[16] Sodi-Pallares et al.,[17,18] Gibert-Queralto and co-workers,[19–21] and others explored the left cardiac cavities with the use of catheter electrodes. Considerable contribution was made to the understanding of cardiac electrophysiology by these studies. However, the electrical phenomena

* From the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, the Department of Medicine, School of Medicine, University of California, Los Angeles, and the City of Hope Hospital, Duarte, California.
† Research Fellow, Los Angeles County Heart Association.
‡ Research Fellow, American Heart Association.

occurring within the myocardial wall remained unexplored; the mode of genesis of electrocardiographic deflections between endocardium and epicardium continued to be unknown.

Our interest in further study of this field was aroused when certain electrocardiographic findings obtained in experimentally produced myocardial infarction in dogs could not be adequately explained by the classic concepts: it was observed that an old infarct confined to the subendocardial myocardium did not alter in any way the records taken directly from the overlying normal epicardium. This was at variance with the prevailing concepts concerning electrocardiographic changes of subendocardial infarction which anticipate a QR type of complex.[22,23] If it is assumed that all layers of the myocardium are equipotent in producing R potentials, then necrosis of the subendocardial layers would be expected to cause the initial segment of the R wave to be replaced by a Q wave. The discrepancy could not be resolved without knowledge concerning what takes place during the process of repolarization in the various myocardial layers individually.

The development of a new approach to the study of ventricular activation by use of needle or "plunge" electrodes in this laboratory, and independently by Scher,[24] Sodi-Pallares[25] and Durrer,[26] opened new vistas to the understanding of electrocardiography. This technic enabled us to register electrocardiographic phenomena at any desired level of the myocardium. Depolarization of the inner layers was shown to produce no R wave. Records obtained from these layers yielded pure QS waves rather than rS waves as had been assumed by classic theories.

These findings afforded a tentative explanation for the previous observation that healed subendocardial infarction in dogs was not associated with electrocardiographic changes. Indeed, necrosis or fibrosis of a portion of the myocardium which does not normally contribute to the genesis of the electrocardiographic deflections could not be expected to alter the electrocardiogram.

The technic of intramural electrocardiographic exploration was considered to be informative and, in fact, indispensable for study of the otherwise inaccessible intramural layers. Since it was noted in several hundred dogs subjected to intramural electrocardiography that the procedure was without hazard, similar studies in human beings were considered feasible and the objective evidence resulting therefrom highly desirable.

A review of the literature concerning intracardiac injection of drugs for the purpose of resuscitating the stopped heart revealed that the procedure of cardiac puncture was without untoward consequences in the hearts revived.[27,28] Accidental puncture wounds of the heart, such as those occasionally encountered in the course of pericardial paracentesis and in stab wounds of the heart, are known to be fatal only if they traumatize an important branch of the coronary arteries, leading to hemopericardium and cardiac tamponade.

Clinically, Ponsdomenech and Beato Nunez in 1951[29,30] suggested a technic of cardiac puncture for direct visualization of the cardiac cavities. They introduced a special trocar forty-five times in thirty patients through a subxiphoid transdiaphragmatic route and found the procedure devoid of significant ill effects. In cardiac surgery, Brock's valvotome or other comparable instruments are thrust through the ventricular wall for division of stenotic pulmonic or aortic valves. Bleeding from the site of the valvotome after it is removed is usually minimal and controllable with fingertip pressure.

The extensive experience accumulated during four years of intramural electrocardiographic studies in dogs led us to regard the procedure as completely safe. Intramural electrocardiography was found to be devoid of hazard not only in normal dogs but also in dogs with the following conditions: acute and old myocardial infarction, experimentally produced bundle branch block, ventricular arrhythmias, experimentally produced arterial hypertension and myocardial failure due to hemorrhagic shock. There were no complications attendant upon cardiac punctures even in dogs dying after prolonged manipulation with production of multiple infarcts. No serious complications occurred in animals subjected to numerous plunges on repeated occasions. Isolated premature ventricular contractions, which were always innocuous, constituted the only ill effect attributable to the puncture with plunge electrodes.

It is to be recalled that the plunge electrode used in this type of study is very small, the size of a 22 to 20 gauge injection needle. The amount of trauma to the myocardium is negligible and the bleeding hazard is practically non-existent

when the coronary arteries are avoided under direct vision.

On the strength of these facts and observations, and since we had no reason to fear that the human heart would be more vulnerable to electrode puncture than the dog's heart, a study of human intramural electrocardiography was undertaken.

MATERIAL AND METHODS

The present report is based on the results of intramural electrocardiography in twelve human subjects. However, prior to initiation of this study two patients who were found to have incurable carcinomas during thoracotomy were subjected to this procedure. This was done primarily to determine the response of the functioning human heart to puncture with our minute plunge electrodes. The electrode was introduced to a depth of 5 mm. in the lateral wall of the heart and then removed. There was no bleeding from the puncture sites and it was noted that under direct vision the coronary arteries could be avoided without difficulty. Continuous, direct electrocardiograms revealed only occasional premature ventricular contractions. Postoperative observation failed to reveal any complications.

Subjects. There were twelve patients in whom thoracotomy was performed for treatment of various conditions: carcinoma of the lung in four; rheumatic heart disease with mitral stenosis in three; carcinoma of the esophagus in one; cardiospasm associated with megaesophagus in one; pulmonary tuberculosis in one; cyanotic congenital heart disease in one and possible constrictive pericarditis in one. There were six males and six females, ranging in age from twenty to sixty-two years.

There was no clinical or laboratory evidence of heart disease in seven subjects. In the remaining five there was clinical evidence of organic heart disease (three of mitral stenosis, one case of possible constrictive pericarditis and one case of congenital heart disease). The patients with mitral stenosis and congenital heart disease did not, however, exhibit any evidences of intrinsic myocardial disease. There were no signs of rheumatic activity.

Electrodes. The electrodes used in this study were similar to those described previously.[31] They consisted of straight 2 inch long pieces of 0.020 gauge tempered silver wire sharpened at the recording tip. The insulating material chosen for this study was G.E. glyptal which is a water/oil resisting rubber cement with very high viscosity. The electrode wire was introduced into the cement and pulled out gently so as to secure a uniform, smooth coating on the wire. By virtue of its high viscosity, the insulating substance withdraws from the sharp tip leaving the very end bare and conductive. When dry, glyptal possesses remarkable pliability, allowing the electrode to be bent or manipulated without losing the continuity of its insulating coating. The other end of the electrode was connected to electrocardiographic lead cables by means of an insulated fine copper wire. The electrodes were sterilized in strong zephiran® solution before use.

Each electrode was scrupulously tested before and after use for evidence of "leak" or defective insulation. The recording tip was chlorided prior to use. The electrodes were marked at 2 to 5 mm. intervals so that the distance between the recording tip and the epicardial surface could be determined with ease. Soft cotton-tipped electrodes were used for recording of the surface potentials.

Recording Apparatus. Two sets of recording apparatus were used: the direct-writing Sanborn Viso Cardiette for continuous observation of cardiac rate and rhythm and the Sanborn Twin-Beam electrocardiograph which is a photographic apparatus with a very high frequency response and capable of operation at paper speeds of 25 mm./sec. and 75 mm./sec. By virtue of its high frequency response and high paper speed, it enabled us to analyse the deflections with considerable precision.

The standard limb lead II was recorded on the upper channel of the Twin-Beam and used as time reference. The direct intramural lead was recorded in both the direct writing Viso Cardiette and the lower channel of the Twin-Beam. The indifferent electrode was connected to Wilson's central terminal forming a unipolar lead. Intramural tracings were recorded at an attenuation of 20X so that an input potential of 20 m.v. caused a 10 mm. deflection.

The procedure was performed in the operating room with patients anesthetized for surgical treatment of their basic diseases. It consisted of introducing the electrode into the myocardium and recording potentials at various depths of the myocardial substance as well as from the ventricular cavity and surface. The area of the left ventricle most commonly used for exploration was the free lateral wall mid-way between the apex and the base. It was found that the electrode entering the cavity from this area would avoid both papillary muscles.

In only one case was the chest opened on the right, for removal of carcinoma of the right lung. In this case intramural electrocardiography was carried out in the infundibular area of the right ventricle. In the remaining eleven cases the procedure was performed on the left ventricle.

An attempt was made to enter the cavity of the ventricle first and then, by withdrawing the electrode slowly, record from various levels of the myocardium. This was done primarily to secure orientation concerning the location of the electrode tip. Generally, the cavity tracing could be recognized rather easily as the depolarization complex obtained therefrom exhibited a pure, symmetric QS followed by an isoelectric S-T segment. Furthermore, in the process of advancing the electrode into the myocardial sub-

stance and toward the cavity it was possible to determine the exact moment when the electrode tip was against the endocardium by the perception of an elastic resistance. For analogy and simplicity, the consistency of the myocardium can be likened to that of Swiss cheese and the consistency of the endocardium to that of cellophane wrapping paper around it. After exerting additional pressure for traversing the endocardium a sensation of "give" could be perceived as the tip entered the ventricular cavity.

It is pertinent to mention at this point that the thickness of the ventricular wall of a heart is considerably greater during life than it is after death. The explanation for this is not quite clear; however, it appears that the amount of blood contained within the myocardium and the tone peculiar to living muscle cells account, at least in part, for this finding. It is not surprising, therefore, that in our studies the normal human left ventricular wall was found to be 25 to 30 mm. thick instead of 10 to 15 mm. found in normal hearts after death.

The records were analysed for the following: (1) configuration of the QRS-T from the cavity, intramural layers and epicardial surface; (2) characteristics of the injury current incident upon introduction of the electrode into the myocardium; (3) time of arrival of the activation wave at various levels of the myocardial thickness and, secondarily, speed of transmission of the depolarization wave through the ventricular wall. The time reference used for this purpose was the beginning of the QRS deflection in the simultaneously recorded lead II.

The procedure in general was not difficult; however, it was more complicated than comparable procedures in the dog due to the following facts: first, the greater vigor and amplitude of cardiac contractions in human beings made manipulation and holding in place of the electrode somewhat tedious; second, the 60 cycle alternating current was a persistent annoyance in the operating room: it was difficult to eradicate in spite of the availability of competent professional assistance; third, the electrode-induced injury current was more persistent in man than in dogs. Although the injury current did decrease in amplitude when the electrode was allowed to remain in place for several minutes, this was not always feasible in surgical patients as it would prolong the operation.

LEFT VENTRICLE (ELEVEN CASES)

Configuration of the Depolarization and Repolarization Complexes. Depolarization complexes: The depolarization complexes were identical in nine cases, and were considered to represent normal pattern of depolarization. In the remaining two cases (both of mitral stenosis) certain departures from normal were encountered which will be pointed out.

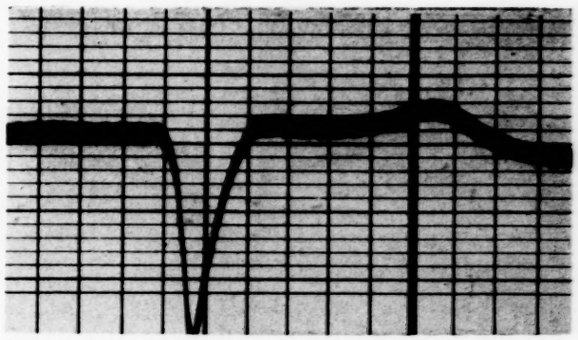

FIG. 1. A typical left ventricular cavity complex with pure QS, isoelectric S-T segment and positive T wave.

The normal cavity depolarization complex consisted of smoothly contoured, pure QS waves with symmetrically ordered descending and ascending limbs. (Fig. 1.) In the two cases of mitral stenosis a notch was present in the descending limb of the QS.

The intramural depolarization complexes differed materially in the subendocardial and subepicardial myocardium consisting in the former of pure QS deflections with no evidence of R wave, and in the latter of rS or qrS. For all practical purposes the myocardial wall seemed to be made up of two zones distinguishable one from the other in the matter of generating R potentials. The first zone, the subendocardial myocardium, was virtually "silent," that is, it did not produce R potentials. Subendocardial QS waves were distinguishable from cavity QS waves by the presence in the former, of small S-T segment elevation ranging in amplitude from 1 to 5 mm. This minimal injury current could be eliminated by allowing the electrode to remain in place for a short time. The second zone, the subepicardial myocardium, was wholly or almost wholly responsible for the genesis of R potentials. The first evidence of R wave usually began at a level almost equidistant from endocardium and epicardium and gradually increased in size as the electrode was moved out towards the epicardial surface. (Fig. 2.) The R/S ratio increased progressively in this zone. On the epicardial surface the depolarization complex consisted of qRs or Rs.

In the two cases of mitral stenosis the notch observed on the descending limb of the cavity QS waves persisted throughout the myocardial thickness.

Repolarization complexes: Cavity and intramural T waves were positive in all cases. Surface T waves, on the other hand, were positive

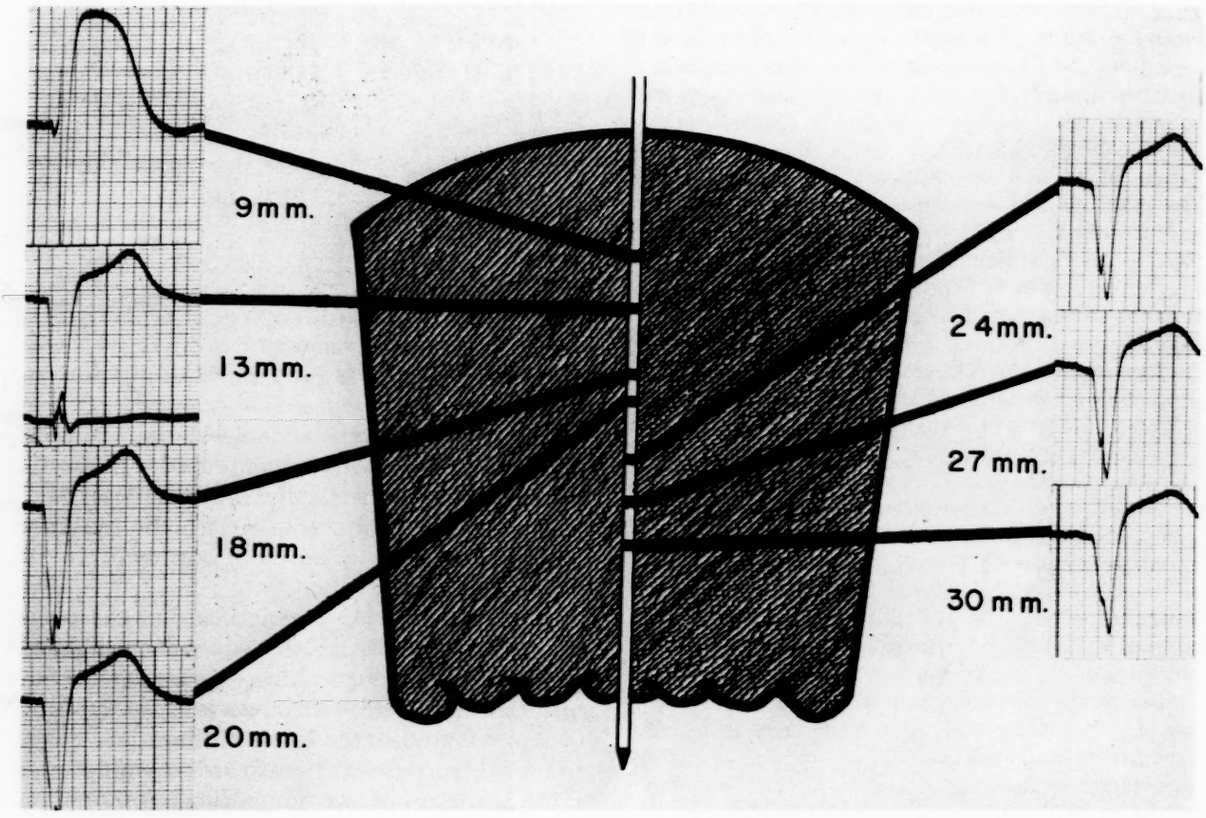

FIG. 2. Records obtained from various depths of the myocardium and from the surface. All the records taken from the inner half of the myocardial thickness are identical in every respect. The depolarization complexes obtained from the inner 15 mm. of the myocardial thickness consist of pure QS waves. At 12 mm. there is a small R wave and an S wave which is smaller than the S wave of the deeper layers. On the surface the complex shows no S wave. The S-T segment is isoelectric in all records taken from the cavity to a distance of 18 mm. from the epicardial surface. S-T segment elevation makes its appearance at 15 mm. below the surface and progressively increases in size as the electrode is moved toward the epicardial surface.

in ten cases (Fig. 3) and flat to slightly inverted in one case. The amplitude of the T waves obtained from cavity, intramural layers and epicardial surface was equal in nine cases. This is considered to be the normal pattern for the T waves. In the remaining two cases, however, there was a gradual change in the amplitude: increase in endoepicardial direction in one and increase in epiendocardial direction in the other. (Fig. 4.)

S-T Segment and the Electrode-induced Injury Current. S-T segments were invariably isoelectric in leads recorded from the cavity. There was slight S-T segment elevation in leads recorded from the inner myocardial layers. As shown in Table 1, the electrode-induced injury current of the subendocardial layers ranged in amplitude from 1 to 5 mm. with a mean value of 2.75 mm. and standard deviation of ± 0.46. Under no circumstances was a monophasic curve or even a high injury current obtained from this portion of the myocardium.

The electrode-induced injury current in the superficial myocardial layers was generally high, ranging in amplitude from 15 to 30 mm. with a mean value of 22.66 mm. and standard deviation of ± 2.19. (Table 1 and Fig. 5.) Monophasic curves were commonly observed in tracings taken from the outer myocardial layers. The injury current in this portion of the myocardium, unlike that of the deep layers, persisted for periods exceeding ten minutes. (Fig. 6.) QRS and T deflections were readily distorted by high injury currents. Consequently, complexes recorded from the superficial myocardial layers which retained their injury current did not always yield to accurate interpretation.

Epicardial surface complexes were obtained by the use of cotton-tipped soft electrodes, hence no S-T segment elevation was observed. How-

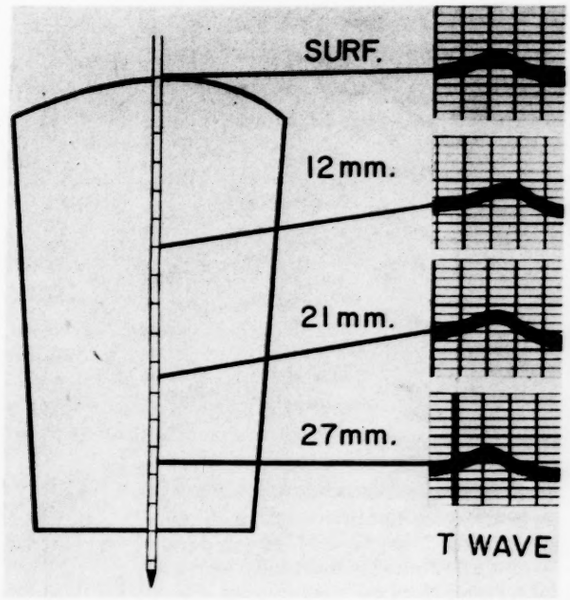

FIG. 3. Intramural and surface T waves obtained from a normal left ventricle. Note that all T waves are identical in direction and amplitude.

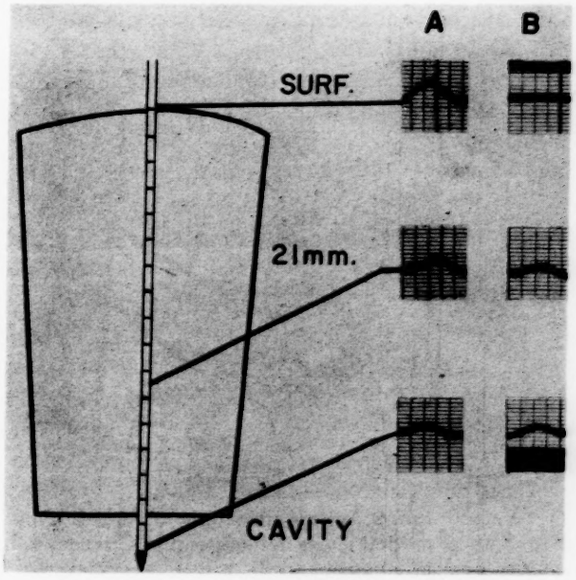

FIG. 4. Cavity, intramural and surface T waves. A, normal left ventricle; note the gradual increase in amplitude from cavity to epicardium. B, left ventricle in a case of mitral stenosis; note the gradual decrease in amplitude from cavity to epicardium.

ever, after the normal complex had been obtained, pressure was applied to the epicardial surface simply by pressing the electrode against the myocardium. This was done in order to determine the amplitude of the artificially produced injury current at the epicardium. It was found that pressure over the epicardial surface always gave rise to an extremely high injury current and a monophasic curve. (Fig. 7.) The amplitude of this type of injury current was far greater than any injury current registered from the intramural layers. Such injury current caused profound distortions in the configuration of QRS and T wave. The most striking alteration in QRS was a significant, sometimes sixfold increase in the amplitude of the R wave. T waves were usually incorporated into the monophasic curve.

TABLE 1
HIGHEST INJURY CURRENT IN TRACINGS (MM.) FROM SUBENDOCARDIUM AND SUBEPICARDIUM

Patient	Subendocardium	Subepicardium
1	3	30
2	3	30
3	3	28
4	5	25
5	2	15
6	1	16
7	1	15
8	?	27
9	?	18
10	4	?
Mean	2.75 ± 0.46	22.6 ± 2.19

Time of Arrival of Impulse at Successive Myocardial Levels and Speed of Impulse Transmission. Since the introduction by Lewis[32] of the terms "intrinsic deflection" and "extrinsic deflection," it has been customary to use the former for time measurements. Activation of the muscle fibers situated immediately under a direct unipolar electrode is said by various authors to be represented by the onset, termination or the most rapidly inscribed segment of the intrinsic deflection.[33,34] For reasons stated elsewhere[35] and not germane to this discussion we have chosen the most rapidly inscribed portion as representative of activation of the myocardial fibers directly in contact with the tip of the plunge electrode and will refer to it hereafter as the "sharp segment." Furthermore, it did not make any significant difference whether the onset, termination or the sharp segment was used.

The time of appearance of the sharp segment of the intrinsic deflection as calculated against a constant time reference (e.g., onset of QRS in simultaneously recorded lead II) varies depending on how early in the process of depolarization the point of electrode contact is activated. The

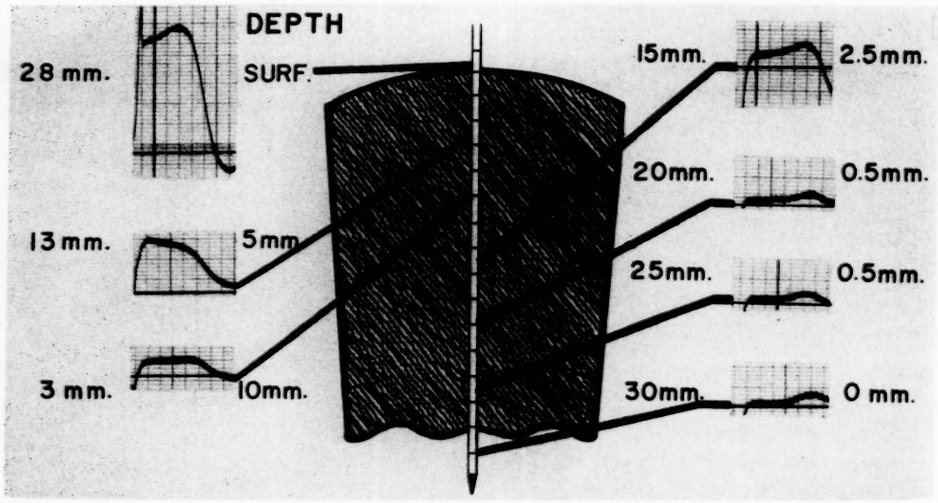

FIG. 5. Injury amplitude at various levels of human heart. Records obtained from all myocardial levels demonstrating absence of injury current in the inner layers between depths of 30 mm. and 15 mm. First evidence of injury current at 12 mm. It gradually increases to become of enormous magnitude at the epicardial surface. Note the concomitant alterations of the QRS complex in surface lead.

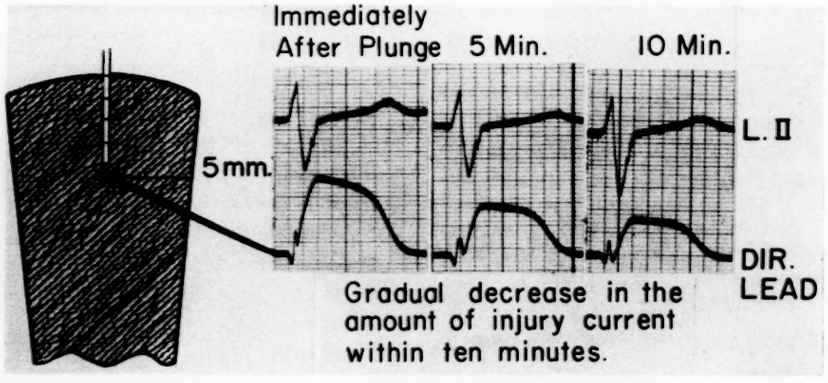

FIG. 6. Very high S-T segment immediately after introduction of electrode. Injury current decreases in amplitude when the electrode is allowed to remain in place for ten minutes.

sequence in which various points or layers of the myocardium are activated therefore can be determined by comparison of the appearance times of their intrinsic deflections. By employing this technic the time of arrival of impulse, that is, the time of activation of the various myocardial layers, was determined. Once the time of arrival of impulse at any two intramural levels with known depths was calculated, the speed of impulse transmission through that portion of the myocardium interposed between the two levels could be determined with ease.

As pointed out earlier in this communication, the subendocardial tracings of normal hearts yielded pure QS waves without very sharp intrinsic deflections. However, the QS waves obtained from the entirety of the subendocardial myocardium exhibited a constant time relationship to the onset of QRS in lead II. Lack of a detectable intrinsic deflection and also lack of a measurable time difference among QS complexes of the various subendocardial layers can be explained on the basis of two possibilities: either the speed of impulse through the subendocardial layers is too fast to be measured with the apparatus of the type used in this study, or depolarization of the myocardial fibers in these layers takes place simultaneously giving rise to electromotive forces that are oriented in multiple directions, hence cancelling each other out. It is suggested that both factors are operative; the high speed of activation causes the action

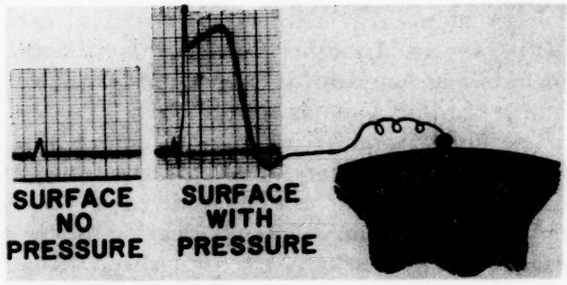

FIG. 7. The complex on the left shows surface potentials as recorded with a soft cotton-tipped electrode. The complex on the right illustrates potentials from the same point on surface after electrode is pressed against the myocardium. Note marked injury current; increase in R amplitude.

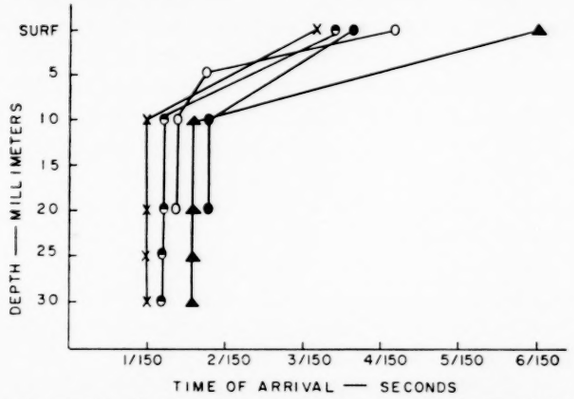

FIG. 8. Numbers on the ordinate represent depth of the myocardial levels in millimeters from which records were obtained in five cases. The numbers on the abscissa represent time intervals in seconds between the beginning of QRS in lead II and the intrinsic deflection in intramural and surface records. The intrinsic deflection of all myocardial layers between depths of 30 and 10 mm. appeared practically simultaneously, indicating a very rapid transmission of impulse through the inner layers. The impulse was relatively slow in the outer layers requiring $^{3}/_{150}$ to $^{5}/_{150}$ of a second to travel through the outer 10 mm. of the myocardium. These values may not be applicable in all instances due to the small number of cases studied.

potentials to be generated almost simultaneously and in multiple directions. The explanation may lie in the fact that, as has been suggested, the Purkinje system penetrates deeply into the subendocardium and conveys branches to muscle fibers present in this zone of the myocardium, hence instantaneous activation of all the muscle cells in contact with rapidly transmitting Purkinje fibers.

In the outer myocardial layers, on the other hand, the speed of impulse transmission ranged from 450 to 1,000 mm./sec. (Figs. 8 and 9.) Admittedly, measurements were extremely difficult in records taken from this portion of the myocardium due to the presence of injury current and obliteration by the injury current of the intrinsic deflections. However, the complexes obtained from the inner portion of the subepicardium, on the one hand, and those registered from the epicardial surface, on the other, displayed distinct intrinsic deflections and were suitable for the purpose of speed calculations.

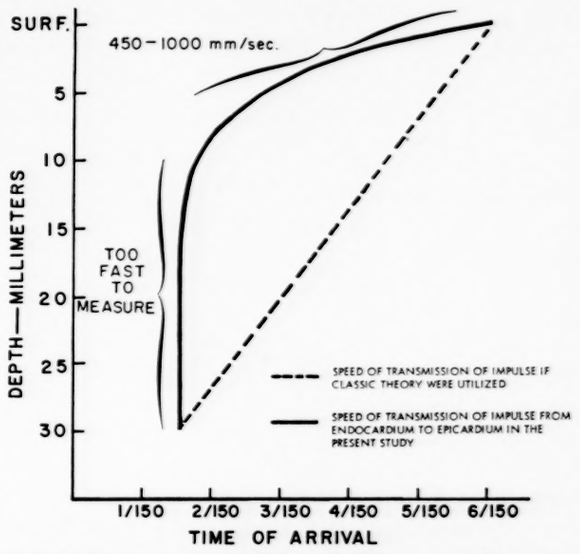

FIG. 9. Same cases as in Figure 8. The speed of impulse transmission through myocardial wall is calculated on the basis of time of arrvial of impulse to various myocardial levels. Note that while the speed in the inner layers is too fast to measure, it is of the order of 450 to 1,000 mm. per second in the outer 10 mm.

RIGHT VENTRICLE (ONE CASE)

A satisfactory intramural exploration could not be made in this case due to unfavorable exposure. The cavity tracing exhibited rS type of depolarization complex associated with a negative T wave. The only two intramural records obtained showed predominantly negative QRS complexes with marked S-T segment elevation which obscured the T waves.

COMMENTS

Comparison Between the Classic Theories and Findings in the Present Study. The prevailing concepts of electrocardiography are based on the assumption that the depolarization process begins in the endocardium and advances at a steady rate towards the epicardium. All layers of the myocardium are supposed to be equipotent in producing depolarization potentials, hence a steady increase in the size of the R wave

from endocardium to epicardium. (Fig. 10.) The direction of injury current according to available experimental and clinical data (Ref. 36 to 41 and others) is said to depend on the location of the injury within the myocardial wall. Thus subendocardial injury is supposed to cause

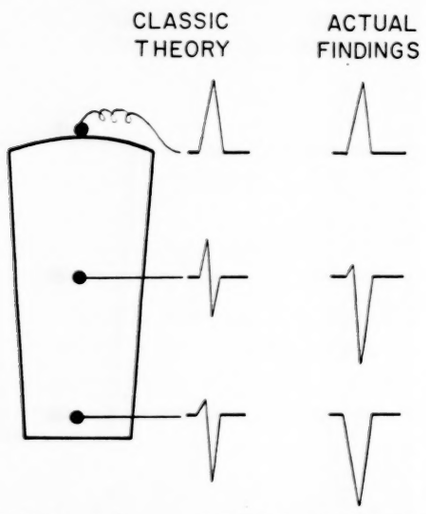

FIG. 10. Schematic representation of intramural and surface QRS complexes according to classic theory (left) and after our findings (right). Note that in contrast to classic theory, no R wave of any size was found in the inner layers. R wave begins at a considerable distance from the endocardium.

S-T segment elevation in leads recorded from the cavity and S-T segment depression in leads taken from the overlying epicardial surface; subepicardial injury is said to do the opposite, that is, produce S-T segment elevation on the surface and depression in the cavity. Furthermore, it is usually granted that all layers of the myocardium are equally capable of generating injury potentials.

The repolarization potentials are supposed to be equal in magnitude and directed opposite the depolarization potentials in any given myocardial cell or muscle strip. It has been inferred therefore that the T vector in a given segment in the myocardial wall is directed opposite the depolarization vector and that all layers are equally potent in generating repolarization forces. The data obtained in the present study are at variance in several respects with these classic theories.

1. *The inner layers of the myocardium do not appear to participate significantly in the genesis of the depolarization forces.* The subendocardial QS waves obtained in these experiments resembled cavity QS waves. The R wave was found to develop almost exclusively in the outer myocardial layers. In other words, the subendocardium was found to be "silent" insofar as the genesis of the R wave is concerned.

The notch observed on the descending limb of the subendocardial tracings in the two cases of mitral stenosis is not to be considered as representing subendocardial depolarization since it was present in the cavity tracings as well. Moreover, the time of occurrence of this notch was late, near the nadir of the QS. If it represented activation of the subendocardial myocardium it would have occurred early, indeed as the first component of the depolarization complexes registered from the subendocardial layers. It may be well to point out further that the amplitude of this notch did not exceed 1 m.v. in direct leads, hence was too small to be registered in the clinical electrocardiogram.

The speed of transmission of impulse through various myocardial layers was not uniform. Measurements made with the use of lead II as time reference showed the speed of impulse transmission in the subendocardial myocardium to be extremely rapid while in the outer myocardial layers it measured between 450 and 1,000 mm. per second.

2. *The reversed flow of current between the inner and outer layers described by Durrer and his associates*[42] *was not encountered in our studies.*

3. *The contribution to the genesis of injury potentials made by the subendocardial myocardium was found to be small.* The amplitude of the electrode-induced injury current in the subendocardial myocardium was negligible in comparison with similar injury current registered from the superficial myocardium. A monophasic curve was never obtained from the inner layers whereas it was a common occurrence in the outer layers. As illustrated in Table I, the mean value for amplitude of the injury current in the subendocardial myocardium was 2.75 mm. compared to the corresponding value of 22.66 mm. in the outer myocardium. Admittedly, the injury current in these experiments was that which was produced upon introduction of the plunge electrode into the myocardial substance, hence possibly different from injury current present in human myocardial infarction. However, there is reason to believe that the injury current present in spontaneously occurring myocardial infarction follows a similar pattern: on the one hand, injury current in experimentally produced myocardial infarction in dogs is generated in the same man-

ner as the electrode-induced injury current in this animal[43] and, on the other, there is a striking similarity between the electrophysiologic behavior of the human and dog's heart.

In most of the studies of intracavity electrocardiography in which a catheter electrode was used (Ref. 11, 18, 19 and others) a marked S-T segment elevation was registered when the catheter exerted pressure against the heart. This finding may be interpreted by some as evidence that the injury potential is produced in the subendocardial myocardium. We would like to point out, however, that a likely explanation for this discrepancy is that the catheter exerts pressure with each systole against the papillary muscles which have been shown to be capable of producing marked injury potentials. It is also possible that by jarring continuously against the myocardium the catheter electrode causes significant damage to the myocardium. These factors do not exist when the plunge electrode is used since, first, the papillary muscles can be avoided by proper selection of the site of exploration and, second, the electrode which is placed in the myocardial wall moves with it rather than against it; hence no jarring.

4. *T waves were identical in the cavity, throughout the myocardial thickness and on the ventricular surface in the majority of our cases.* In nine cases there was no gradient of potential across the myocardial wall insofar as the repolarization process was concerned. In one case of normal heart T waves showed a tendency to increase in amplitude in the endoepicardial direction. In one case of mitral stenosis the reverse phenomenon was found. We are cognizant of the fact that surface T waves may and often will change direction and amplitude upon exposure of the epicardial surface to room air, hence surface T waves obtained in the present study may not have been the true representation of the repolarization process as registered at the epicardial level; however, we have reason to believe, on the basis of our animal experimentations,[44] that exposure of the epicardial surface does *not* alter subendocardial and intramural T waves. The fact remains therefore that human cavity and intramural T waves are equal in magnitude in the majority of cases, a finding which is at variance with the classic concepts of electrocardiography. In most of the studies in which the left ventricular cavity was explored with the use of an intracardiac catheter electrode in human subjects[17–21] the T waves were found to be negative; however, in none of these cases was the epicardium explored by the direct method, hence no information was obtained concerning the direction of the T wave on the corresponding epicardial surface. While it is not impossible that the T waves in these cases were also negative at the epicardial surface, we do not believe that our data concerning T waves in this study are sufficiently conclusive to permit us to engage in the discussion of these discrepancies. Moreover, the general anesthesia used in subjects of the present study may have conceivably altered the vulnerable process of repolarization, another factor which may limit the value of our findings in respect to the T waves. According to classic theories, one would expect to find T waves of opposite directions in the cavity and on the epicardial surface and transition forms within the wall. In our studies, however, a biphasic T wave was never encountered in intramural leads. Furthermore, in experimentally produced myocardial infarction in dogs no significant abnormality was found in the intramural T waves recorded from the deep ischemic zone; T wave inversion appeared to be accounted for by repolarization changes of the outermost myocardial layers. By reason of the analogy found between experimentally produced infarction in dogs and spontaneously occurring infarction in humans, it is conceivable that the T wave inversion in human patients also represents repolarization aberrations of the outer myocardium and that ischemia of the deep myocardial layers may not alter T waves appreciably.

If our views concerning the similarity between experimentally produced infarction in dogs and spontaneously occurring human myocardial infarctions are valid, then our findings in the study of the former[35,43–48] will be applicable to the latter. Accordingly, old infarction limited to the subendocardial region will not be expected to alter the QRS complex. QRS changes will occur only when the superficial myocardium is involved. The presence of abnormal Q waves will indicate a lesion of the superficial myocardium. The presence of abnormal QS waves will represent through-and-through infarction with complete transmural death of the involved portion of the myocardium ("coronary QS waves") or transmural lesion interspersed with islands of living tissue ("mural type QS waves"). Subendocardial injury will not cause significant S-T segment displacement in the epicardial leads as the injury potentials generated in this

portion of the myocardium are too small to be registered. Subepicardial injury, on the other hand, will always be associated with marked S-T segment elevation on the corresponding surface. No T wave changes will be encountered in subendocardial ischemia since ischemia of this zone is not accompanied by significant repolarization aberrations. T wave changes will be accounted for by ischemic changes of the superficial myocardium.

An interesting finding in dogs which may have a counterpart in human beings is the type of S-T segment depression recorded at the epicardial surface and apparently generated in the superficial myocardium.[43] This type of S-T segment depression, which may be termed "primary epicardial," is distinguishable from the so-called reciprocal S-T segment depression by the fact that it is not due to S-T segment elevation on the opposite wall. It is an isolated finding which usually occurs at or near the margin of subacute or old infarcts. It is unlikely that this type of S-T segment depression is reciprocal to subendocardial injury as the latter has been shown not to generate sufficient injury potentials. Moreover, plunge electrodes placed in the subendocardium subjacent to the area of "primary epicardial" S-T depression failed to show the presence of S-T elevation in the subendocardium. The mode of genesis of this S-T depression is not known; however, its occurrence commonly near a subacute infarction speaks in favor of its being due to minor circulatory changes giving rise to biochemical alterations in the subepicardial myocardium.

This type of "primary epicardial" S-T depression, if substantiated in human subjects by more direct studies in the future, may explain the S-T depression found in angina pectoris and coronary insufficiency. Indeed, our findings concerning the relative silence of the subendocardium in generating injury potentials make one wonder how S-T segment depression of angina pectoris and coronary insufficiency could be accounted for by potentials generated in the injured subendocardium. It is suggested tentatively that S-T depression of angina pectoris and coronary insufficiency is most likely accounted for by injury potentials generated in the superficial myocardium as a result of ischemia or other changes.

Discrepancies Between Clinical and Electrocardiographic Findings. If all layers of the myocardium contributed equally to the genesis of electrocardiographic deflections then injury or necrosis of any layer, whether subendocardial or subepicardial, would alter the electrocardiogram; the degree of electrocardiographic alteration would depend on the thickness of the involved layer. However, certain experimental and clinical observations are incompatible with this concept of "electrical equipotence" of electrocardiography. Thus, Boyd and Scherf[49] in 1940 noted that traumatic injury to the subendocardial myocardium produced few electrocardiographic changes while surface lesions altered the tracing profoundly. Kisch[50,51] and Kisch, Nahum and Hoff[52] observed that with the use of KCl as the injurious agent, subendocardial injury produced very little S-T segment changes while application of quantities of KCl incomparably smaller than those injected into the subendocardium gave rise to marked S-T changes. Pruitt, Barnes and Essex[53] experienced difficulty in producing electrocardiographic changes by injuring the subendocardial myocardium. Thus there was prior evidence that the subendocardial myocardium did not produce as much injury potentials as did the subepicardial myocardium. To our knowledge, comparable information concerning the relative contribution of these layers to the genesis of depolarization potentials was lacking before the advent of intramural exploration. The human myocardium in its intramural layers had not been approached; the theories concerning the spread of activation through the human myocardium were largely inferential.

Clinically, however, Levine and Ford in 1950[54] reported six cases of subendocardial infarction, with autopsy confirmation, in which the electrocardiogram had shown no QRS changes. We have encountered at postmortem examination two cases of healed subendocardial infarction in which an electrocardiogram taken prior to death had failed to show QRS changes. QRS changes are rare in inflammatory processes involving the subendocardial myocardium, such as occur in some infectious endocarditides and in the condition known as cardiovascular collagenosis with parietal endocardial thrombosis,[55] in the latter disorder necrosis extends into the myocardial substance without giving rise to QRS changes. Similar discrepancies are encountered in chronic processes involving the subendocardial myocardium, such as endocardial fibroelastosis and old subendocardial infarction. In endocardial fibroelastosis, fibrosis

encroaches upon a significant portion of the subendocardial myocardium, causing intractable congestive heart failure and death, yet in most of the reported cases the QRS complexes remained unchanged.[56,57]

In contrast to failure of the electrocardiogram to reveal subendocardial damage, changes involving the subepicardial myocardium are almost always associated with significant alterations in all components of the electrocardiogram. Acute pericarditis gives rise to marked S-T segment and T wave changes; chronic constrictive pericarditis encroaching upon the superficial myocardial fibers reduces the amplitude of the R wave.[58–60] Levine and McLemore,[61] in an analysis of twenty-six cases of surgically proved chronic constrictive pericarditis, found marked QRS changes "quite diagnostic (four cases) or compatible with or suggestive (eight cases) of old myocardial infarction." We believe, on the basis of our experimental work in animals and human subjects, that the explanation for the marked QRS changes seen in some cases of chronic constrictive pericarditis is the extension of fibrous tissue into the outer myocardial shell which is normally responsible for the genesis of R potentials. If one compares endocardial fibroelastosis with constrictive pericarditis, both of which invade the adjacent myocardium, one is struck by the fact that the former produces little or no electrocardiographic changes whereas the latter is always accompanied by significant electrocardiographic alterations. These observations can be explained by the findings in the present study in which normal superficial myocardium was found to be predominantly responsible for the genesis of electrocardiographic deflections in general, and the R wave in particular, while the subendocardial myocardium was virtually "silent" from the standpoint of generating electrocardiographic forces.

General Clinical Applications. It is to be pointed out at the outset that the investigations on which this presentation is based were direct studies performed on the heart, as were the studies of the normal electrocardiogram and those after experimental production of myocardial infarction in dogs. No attempt was made to correlate the deflections so obtained with those recorded from the body surface in the same subjects. The studies were intended merely to examine, by the most direct method heretofore employed, the genesis of electrocardiographic deflections. The complexes obtained at the body surface represent, according to Wilson,[33] "the potential difference over the epicardial surface that would exist if the heart were to be completely exposed and surrounded by air." Undoubtedly, however, the intramural potentials contribute to those registered at the epicardial surface. Since the latter is the only part of the heart which is in direct contact with the surrounding tissues, it is not illogical to state that the deflections registered on the body surface are determined exclusively by the potential differences present at the epicardial surface.

To what extent the epicardial surface potentials are transmitted to the body surface and what the relationship between epicardial surface and body surface potentials is remains far from clear. However, as Wilson[33] stated, "the potential variation of a given part of the precordium in this animal (dog) are similar in every respect to those of the underlying portion of the anterior ventricular surface" and "one may justifiably conclude from the results of such experiments that *within certain limits* the principles that apply to the interpretation of the ventricular complexes of unipolar direct leads also apply to the interpretation of the ventricular complexes of the unipolar precordial leads." Therefore our findings concerning the silence of the subendocardial myocardium and predominance of subepicardial myocardium are within certain limits directly applicable to clinical, particularly precordial electrocardiograms.

This is true apparently because of the relative proximity of the precordial chest wall to the heart and especially to its anterior wall, on the one hand, and more favorable conduction through the chest wall than through the lung tissue, on the other. The precordial leads, V_1 to V_4, are so close to the anterior surface of the ventricles as to be considered specific for lesions involving this part of the heart. Lesions involving the posterior aspect of the heart affect these leads to a much lesser degree since the distance between electrode positions V_{1-4} and posterior epicardial surface is several times greater than the distance between the positions V_1 to V_4 and the anterior epicardial surface. According to Poisson's Integral, the "potential of a given dipole as determined at a certain point within its electromotive field will vary in inverse relationship to the second (or third) power of the distance of this point from the center of the dipole."[33] It follows that while close or

"semi-direct" leads such as V_{1-4} are relatively specific for the subjacent myocardial wall, remote limb leads especially aVF reflect the totality of the heart because the distances separating these lead positions from all parts of this organ are practically equal. Leads intermediate between semi-direct and limb leads, namely lateral chest, posterior chest and abdominal leads, may be regarded as transitional insofar as their specificity for the subjacent myocardium is concerned. Consequently, unlike the precordial leads to which our findings are probably directly applicable, the limb leads may or may not reflect the phenomena occurring in a limited area of the epicardium. That is to say, while the presence of an abnormal electrocardiographic complex, for instance coronary QS wave representing a small infarct on the anterior myocardial wall, results in a similar finding in the precordial electrocardiogram in a significant proportion (if not all) of the cases, a coronary QS wave from an infarct of the same size on the diaphragmatic surface is less likely to cause QS waves in the left leg lead. Therefore, in applying the findings of this study and our previous direct studies on dog's heart to the clinical electrocardiogram it may be well to bear in mind that the findings are most directly applicable to the "semi-direct" leads; the applicability decreases as the distance between the lead position and the heart increases. To be sure, this rule holds true for all the studies performed directly on the heart, a fact that has long been recognized.

Diagnosis of Subendocardial Infarction. On the basis of the facts and deductions outlined in the foregoing paragraphs we have set up and used certain criteria for the clinical diagnosis of acute and old subendocardial infarction. We have made this diagnosis in a group of patients in the past three years. Two patients of this group have died and postmortem examinations proved the diagnosis to be correct (the case histories will be the subject of a future report). It is for this reason that we feel justified in presenting our criteria as a working basis for the clinical diagnosis of subendocardial infarction.

Acute subendocardial infarction: This diagnosis may be made when such clinical symptoms of myocardial infarction as typical pain with evidence of tissue necrosis with or without congestive heart failure are associated with normal QRS complexes provided that adequate exploration of the chest and abdomen is performed. Admittedly, infarction Q waves may fail to show if a through-and-through infarction involves only a small portion of the epicardial surface; however, it is believed that an infarction large enough to give rise to clinical and laboratory evidences of tissue necrosis is more likely than not to cause abnormal Q waves. We have observed two patients with clinical symptoms of classic myocardial infarction in whom electrocardiograms showed S-T and T changes with normal QRS complexes. The diagnosis of acute subendocardial infarction was substantiated by evidence of tissue necrosis, namely, sustained elevation of white count, sedimentation rate and transaminase blood levels.[62] S-T segment depression and T wave inversion, when present, lend support to this diagnosis.

Not infrequently during the acute stage of subendocardial infarction the hemodynamic alterations propagate to the superficial myocardium and create a transient electrocardiographic picture indistinguishable from that of a through-and-through infarct, namely, infarction Q waves and S-T segment elevation. Under such circumstances the correct diagnosis can be made only in retrospect during the recovery stage of infarction. In this period the infarction Q waves disappear and QRS complexes return to normal as the superficial myocardium overlying the infarcted subendocardium regains its normal circulation. Here again one may argue that return of the normal QRS complexes may be due to "shrinkage" and reduction in size of the through-and-through infarct rather than the mechanism suggested. This argument is probably not valid inasmuch as the return of normal QRS complexes takes place long before fibrosis and "shrinkage" could be expected to have developed (within two to three days as seen in some cases).

Old subendocardial infarction: This type of infarction *per se* has no characteristic electrocardiographic representation, provided that conduction of impulse has not been interfered with. A diagnosis can be made, however, in the light of previous observations and a diagnosis of subendocardial location of the infarct during its acute stage. In some instances an extensive old subendocardial infarction can interfere with myocardial functions severely enough to give rise to progressive, intractable congestive heart failure. Therefore, although the diagnosis of a subendocardial scar in an asymptomatic patient may not imply important consequences,

it is of significant value in patients suffering from congestive heart failure. It is suggested that the diagnosis of old subendocardial infarction be entertained in any patient suffering from progressive congestive heart failure for which no obvious cause can be found and electrocardiograms show normal QRS complexes. This diagnosis is particularly apt to be correct if there is history of coronary pain suggestive of myocardial infarction.

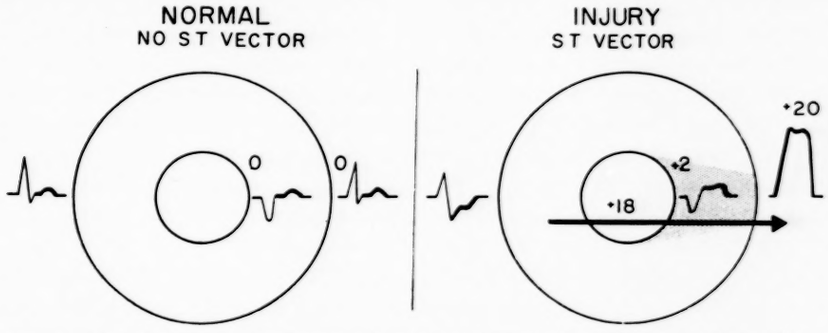

FIG. 11. Orientation of injury current vector. Diagrammatic cross section of the normal heart on left and heart with transmural injury on right. No S-T vector is present in normal heart. In the presence of transmural injury, there are more injury potentials in the outer layers than in the inner layers, hence an injury potential gradient. If of sufficient magnitude, this vector affects the opposite surface in a negative sense and creates S-T segment depression. The numbers used are arbitrarily chosen to indicate the relative magnitude of injury potentials. The dotted area represents injury.

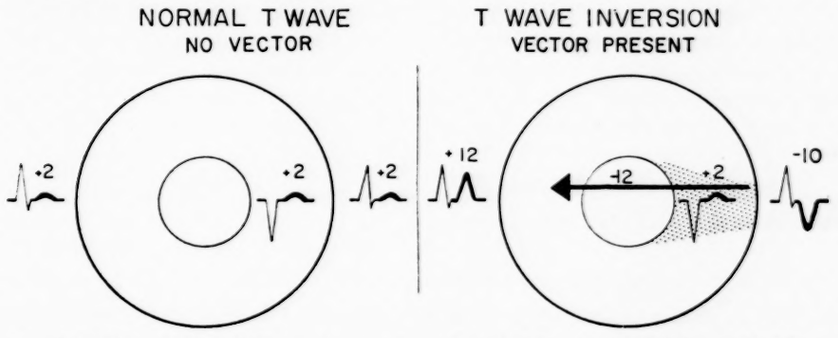

FIG. 12. Orientation of T vector, constructed on the same basis as Figure 11. Normal heart on left, heart with ischemic zone on right. Note that subendocardial T wave remains unchanged in spite of ischemia whereas surface T wave becomes deeply inverted, hence a T vector. Note also orientation of T vector and its influence on leads taken from areas overlying the ischemic zone and areas opposite ischemia. The dotted area represents ischemia.

The Question of S-T Vector. As already indicated, the injury potentials resulting from a given agent (introduction of the plunge electrode, through-and-through infarct) are far greater in the outer myocardial layers than in the subendocardial myocardium. There seems to be a gradual increase in the amplitude of S-T segment elevation from endocardium to epicardium. When plunge electrodes were placed at various points in many intramural layers in the entire zone of experimentally produced through-and-through infarcts in dogs, it was found that the pattern just mentioned in relation to relative magnitude of injury potential was present over the entire area deprived of its blood supply. In other words, it appeared as if the myocardial wall in the injured zone was constructed of innumerable sheets of muscle superimposed one upon another, with a progressive increase in the amount of injury potentials contained in those sheets. It is conceivable that the same is true in human myocardial infarction. Under such circumstances there will be potential differences between the adjacent sheets of the myocardium, thus giving rise to a vector force directed towards the surface of greatest positivity, that is, the epicardial surface. (Fig. 11.) Leads taken from areas overlying such epicardial

surface yielded S-T segment elevation and leads taken from the opposite surface showed reciprocally depressed S-T segments.

A similar statement may be made in relation to the T wave negativity. If the degree of T wave negativity in human myocardial infarction increases progressively from endocardium to epicardium, as was found to be the case in some cases of experimentally produced through-and-through infarct in dogs, then by employing the same argument as that relating to the injury forces, it may be inferred that the vector accounting for negativity of the T waves on the area of infarct is produced by repolarization differences that exist between the adjacent myocardial layers within the ischemic zone. (Fig. 12.) Such a vector, directed away from the ischemic epicardium and toward the ischemic endocardium, accounts for the increase in positivity of the T waves recorded over the opposite wall.

SUMMARY AND CONCLUSIONS

Intramural electrocardiography was performed in twelve patients subjected to thoracotomy for treatment of various intrathoracic abnormalities. The left ventricle was studied in eleven cases and the right ventricle in one. The procedure was found to be completely devoid of hazard.

On the basis of our observations and analysis of our data, the following conclusions seem to be justified:

1. Tracings obtained from the subendocardium exhibit pure QS waves; the positive component of the depolarization complex is generated wholly or almost wholly in the outer myocardial layers. The subendocardium therefore appears to be electrocardiographically silent in respect to the genesis of positive depolarization potentials.

2. The "electrocardiographic silence" of the subendocardium explains why QRS complexes are not altered in pure subendocardial infarction and other conditions involving this portion of the myocardium. Pathologic conditions involving the epicardial portion of the myocardium, such as inflammatory pericardial effusion and constrictive pericarditis, lower the amplitude of the R wave. Endocardial fibroelastosis encroaching upon the subendocardial myocardium and producing a situation comparable to constrictive pericarditis (the difference being in the location of the fibrous lining) causes very little if any QRS changes. No clinical or prognostic inference can be drawn from the degree of R wave changes; rather prognosis must be based on the composite clinical picture.

3. The speed of impulse transmission through the human myocardial wall is not constant. It is found to be very fast in the inner layers (the "silent zone") and of the order of 450 to 1,000 mm./sec. in the outer layers.

4. The subendocardium is also shown to be "sluggish" in generating injury potentials. While a given type of injury, for example injury produced by introduction of the plunge electrode, in the outer layers causes very marked S-T segment elevation, the same injury fails to produce any significant displacement of the S-T segment in the deeper layers. It follows from this and from the animal experiments done in this laboratory that profound injury to the subendocardial myocardium resulting from a variety of conditions, such as coronary insufficiency, myocardial infarction or certain types of acute endocarditis, does not give rise to significant quantities of injury potential, hence little or no S-T segment displacement. Injury to the outer myocardial layers, on the other hand, produces marked S-T segment elevation such as that seen in through-and-through myocardial infarction and acute pericarditis.

5. It is suggested that S-T and T changes commonly found in subendocardial injury may be due to certain functional alterations that take place in the outer myocardial layers. The nature of these alterations has not yet been defined; however, it is possible that it is biochemical in nature, resulting from the hemodynamic changes ordinarily accompanying subendocardial injury. The S-T segment depression resulting from such biochemical changes is tentatively termed "primary epicardial S-T depression" to distinguish it from that type of S-T depression which is reciprocal to elevation on the opposite wall.

6. Under the conditions of these experiments T waves were positive in the cavity and intramural leads. Surface T waves were positive in the majority of cases and flat to inverted in occasional cases. There seemed to be no gradient of potentials between repolarization forces present in the cavity, intramural layers and the epicardial surface in the majority of instances.

7. The presence of a normal or almost normal electrocardiogram in the face of clinical

evidence of profound myocardial damage (acute or old) speaks in favor of subendocardial location of the myocardial lesion. Marked electrocardiographic changes, on the other hand, may or may not bear a quantitative correlation to the degree of myocardial infarction inasmuch as pronounced electrocardiographic changes can represent only minor subepicardial damage.

8. Caution must be exercised in inferring prognostic implications from the electrocardiogram alone. Consideration of the clinical picture remains of utmost importance.

9. Certain working criteria for the diagnosis of acute and old subendocardial myocardial infarction are suggested.

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The Splitting of Heart Sounds*

A Spectral Phonocardiographic Evaluation of Clinical Significance

VICTOR A. MCKUSICK, M.D., W. PAUL REAGAN, M.D., GEORGE W. SANTOS, M.D., *and* GEORGE N. WEBB

Baltimore, Maryland

In selected instances splitting of heart sounds as detected with the stethoscope may be useful in cardiac evaluation. Because of the several conditions which can closely simulate splitting of the valve sounds (S-1 and S-2), this finding can also be confusing; how specific it is, as far as indicating disease and type of disease, is often not certain. Spectral phonocardiography, for reasons to be described in detail, is a useful tool for the re-examination of this problem.

Splitting of heart sounds results from separation of individual components normally present. "Reduplication" (or "duplication") is an unphysiologic designation. There is obviously no echo phenomenon as is suggested by the term; the heart sound is not reproduced.

Advantages of Spectral Phonocardiography in Study of Splitting. Elsewhere[1-3] the principles of the method for displaying and analysing of cardiovascular sound by means of the Bell sound spectrograph have been described in detail. In brief, the method produces recordings in which time, frequency and intensity are each represented in detail. Time is on the abscissa as in most physiologic tracings. The ordinate in these displays, unlike conventional oscillographic phonocardiograms, is frequency, not intensity. Intensity is represented by degree of blackness in any given portion of the recording. A frequency span to 750 cycles per second has usually sufficed.

The electrocardiogram and the respiratory mark have been used for timing purposes in these studies. The importance of recording respiration in any study of splitting of heart sounds resides (1) in the necessity of differentiating normal inspiratory splitting and (2) in the opportunity for identifying the basis of the split afforded by the effects of respiration upon splitting.

The spreading of frequency results in at least three advantages of spectral phonocardiography, the first of which is of primary pertinence to this particular study: (1) Identification of the separate constituents of the heart sounds is facilitated when the frequency spectrum is spread out because the constituent parts of the sound tend to show separation at some frequency levels, if not at other or all levels. For example, merging of the components at the lower end of the frequency scale tends to be the rule because of the high intensity of the vibrations in that range; on the other hand, higher in the frequency scale where intensities are less great the separate parts are more likely to be distinguishable. (2) Quality (timbre) is displayed and given physical definition. This property of the spectral phonocardiogram was used in a study of musical murmurs published elsewhere.[4] (3) The great dynamic range of cardiovascular sound—the intensity range from faintest to loudest sounds in the same patient and at the same auscultatory locus—is better encompassed[5] with simultaneous display, for example, of a very loud murmur and a very faint one in more nearly their true proportions.

Figure 1A shows the demonstration of splitting of heart sounds by this method. Filter system C (with passbands of intermediate width) is the one used in most of these studies since it appears to provide satisfactory simultaneous resolution in both time and frequency.[1] Even better time resolution (with some sacrifice of frequency detail) can be attained by using a filter system with wider passband characteristics (filter E). In the recording with the wider filter system E the individual components of the second sound can be identified in every cycle.

Splitting of heart sounds involving an interval of as little as 0.01 second between constituent

* From the Department of Medicine, Johns Hopkins University School of Medicine and Johns Hopkins Hospital, Baltimore 5, Maryland.

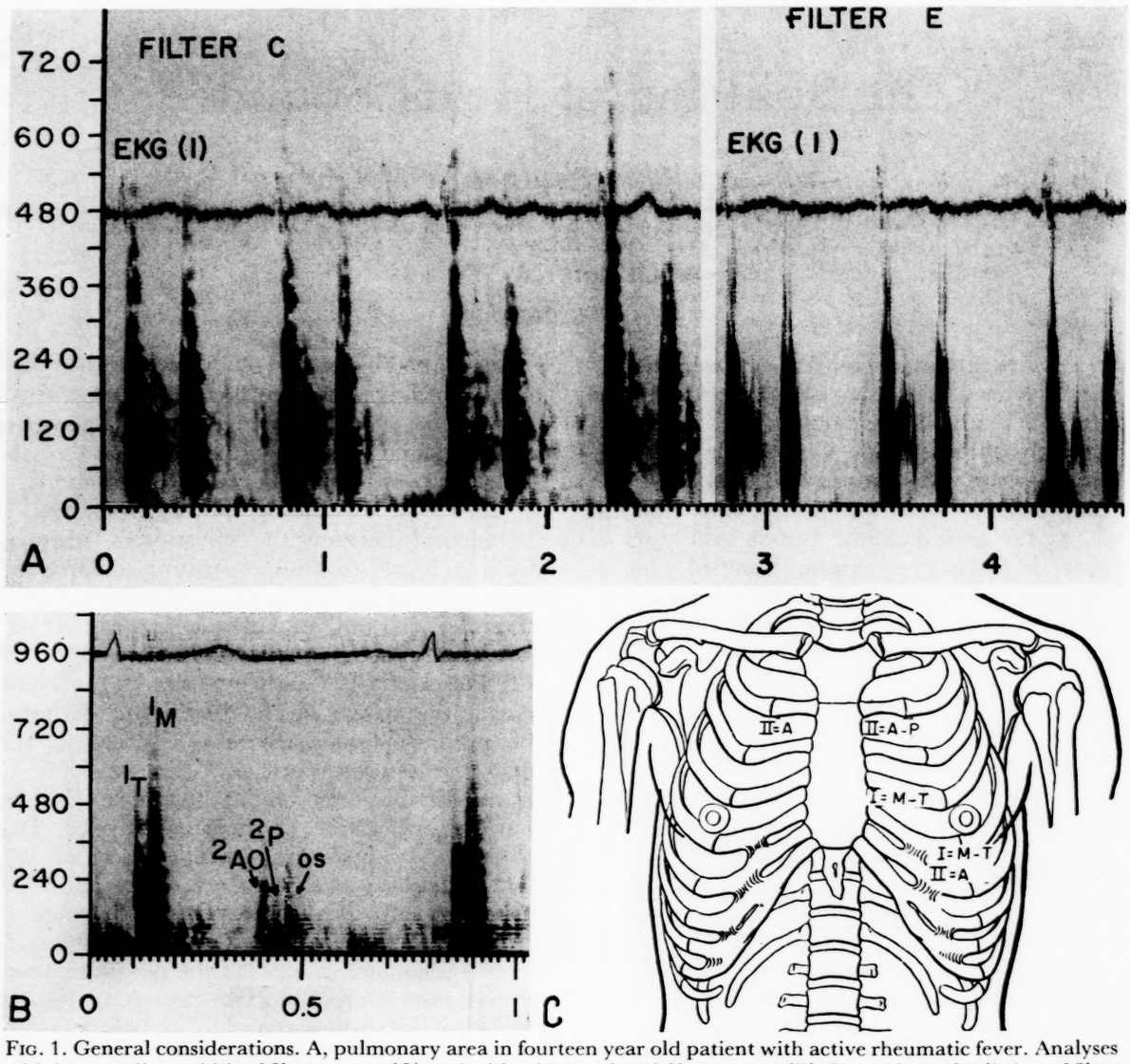


FIG. 1. General considerations. A, pulmonary area in fourteen year old patient with active rheumatic fever. Analyses with intermediate width of filter system (C) and with wide passband filter system (E). B, artefactual splitting of filter origin. Both the tricuspid closure sound (T) and the mitral closure sound (M) appear to be split. C, schematic representation of the normal constitution of the heart sounds (after Leatham).

elements is demonstrable by spectral phonocardiography. Elsewhere[6] we have presented analyses of the sounds produced *in situ* by the Hufnagel ball valve placed in the aorta for the treatment of aortic regurgitation. Although there is only one ball in the artificial valve, it impinges on three corners in opening. Splitting of the opening sound may result from the ball first striking one corner, then the others. Similarly in closing, although the ball becomes impacted on a circular seat, it may well strike one point of this circle, then complete the closure.

Figure 1B presents a source of artefactual splitting in spectral phonocardiograms. If the amplification of the signal put through the filter system is excessive one gets two peaks from each sound. In essence the filter system is activated twice, when the signal first hits it and again during decay of the signal. The recording was made from the apex in a patient with mitral stenosis. True splitting of the first heart sound occurred due to delay of the mitral closure sound. Also both the tricuspid and the mitral closure sounds are split. That the latter splitting is artefactual is suggested by the exact duplication of the harmonic pattern in each of the split components.

The experience reported here is selected from

a total experience with about 700 cases of heart disease, mainly valvular or congenital. In addition about thirty normal subjects have been studied.

Constituents of Normal Heart Sounds. Prior to a discussion of split heart sounds should be a consideration of the constitution of the normal sounds. (Fig. 1C) The studies of Leatham,[7] using oscillograms recorded simultaneously from two or more areas, have done much to elucidate this subject.

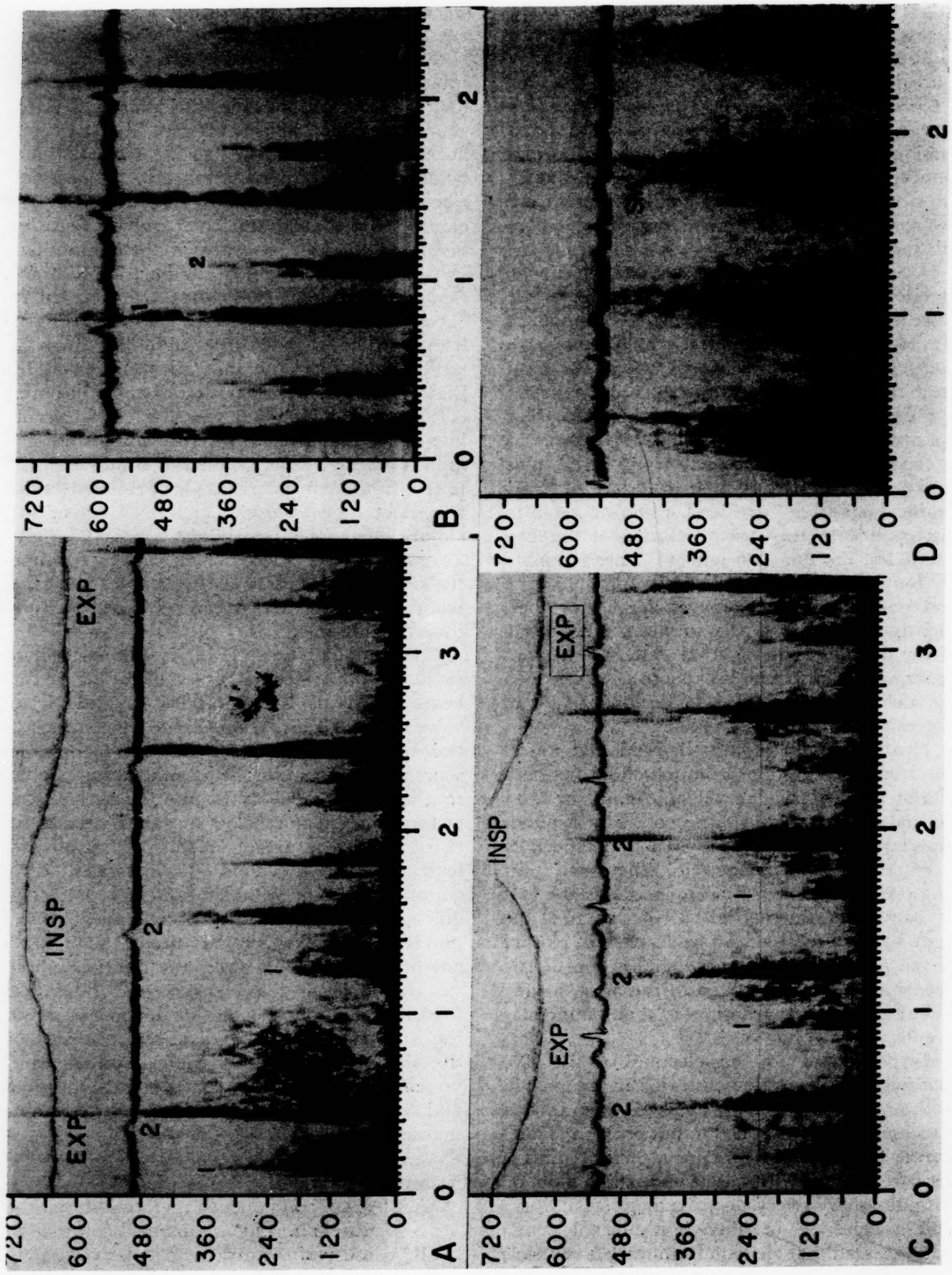
It appears that the normal second aortic sound is almost exclusively the result of aortic valve closure. On the other hand, the pulmonary second sound is contributed to by closure of both the pulmonary and the aortic valves. In most normal subjects inspiration results in a splitting of the pulmonary second sound. (Fig. 2A.) This is a result of delay in pulmonary valve closure as a consequence of increased right ventricular stroke volume, that is, it is a variety of "mechanical splitting" (*v. seq.*) resulting from a discrepancy in the stroke volumes of the two ventricles. The double origin of P-2 has adequate anatomic basis in the proximity of the aortic and pulmonary valves, one behind the other, slightly to the left of the sternum. Knowledge of the double origin of "P-2" removes the confusion which otherwise is likely to be occasioned by such findings as "P-2 louder than A-2" in systemic arterial hypertension.

The first sound in the tricuspid and mitral areas has contributions from the closure of both sets of atrioventricular valves. Again, in most normal subjects slight splitting of the first sound, especially in the tricuspid area and especially in expiration, is demonstrable. When such splitting occurs the mitral closure is usually the first of the two constituents. The second sound at the apex has its origin almost exclusively in closure of the aortic valve. As a generalization, aortic events are well transmitted to the apex, at any rate they are better transmitted than pulmonary events.

Asynchronism in the ejection of the two ventricles has been demonstrated in the past in both animals[8] and man.[9] Electrokymography is a technic recently applied to this problem. Comparing the onset of the major ascending limb of the carotid pulse with the corresponding point on the pulmonary artery electrokymogram, Ellinger and associates,[10] in sixty-eight normal young adults, found that ejection from the left ventricle began first in thirty-three subjects by .01 to .03 second, from the right ventricle first in twenty-one subjects by a similar interval, and from both ventricles synchronously in the remaining subjects. On the other hand, using a similar method Luisada and Fleischner[11] found right ventricle ejection had precedence in all of eight normal subjects by .025 to .03 second. Such demonstrations of asynchronism of the onset of ejection cannot be translated directly to time of closure of the atrioventricular valves. Because of higher diastolic pressure in the aorta than in the pulmonary artery isometric contraction (after closure of the atrioventricular valves) might be expected to be longer in the left ventricle than in the right. By such a mechanism it is possible that mitral closure might slightly precede tricuspid closure and still onset of ejection from the left ventricle would occur later than that from the right. Some studies[12] indeed suggest that isometric contraction is longer in the left ventricle. On a rational basis, precedence of tricuspid closure over mitral closure might be anticipated since the right atrium contracts before the left, and by the time the ventricles contract the tricuspid leaflets have had time to reach a slightly more closed position than the mitral.

Conventional oscillographic phonocardiography has purported to show contributions to the heart sounds of several origins in addition to valve closure. It is best to consider the enumeration of these factors as a catalogue of possible sources of contributions. It is difficult to imagine that what is scarcely at the most more than two or three lines in an oscillogram can be picked out and indicated as arising in this or that physiologic event. The evidence for significant contribution of some of these factors is not convincing. Some of the alleged components may, however, be exaggerated under pathologic conditions as, for example, the ejection vibrations in arterial hypertension and dilatation ("early systolic click") and the opening sound of the atrioventricular valves in the presence of fibrosis of those structures (mitral and tricuspid "opening snap"). The contributions, possible and certain, to each sound can be listed in this manner:[13]

1. First heart sound
   - A. "Atrial components": vibrations in the ventricle in response to atrial contraction
   - B. Closure of the atrioventricular valves
   - C. Vibrations of the contracting myocardium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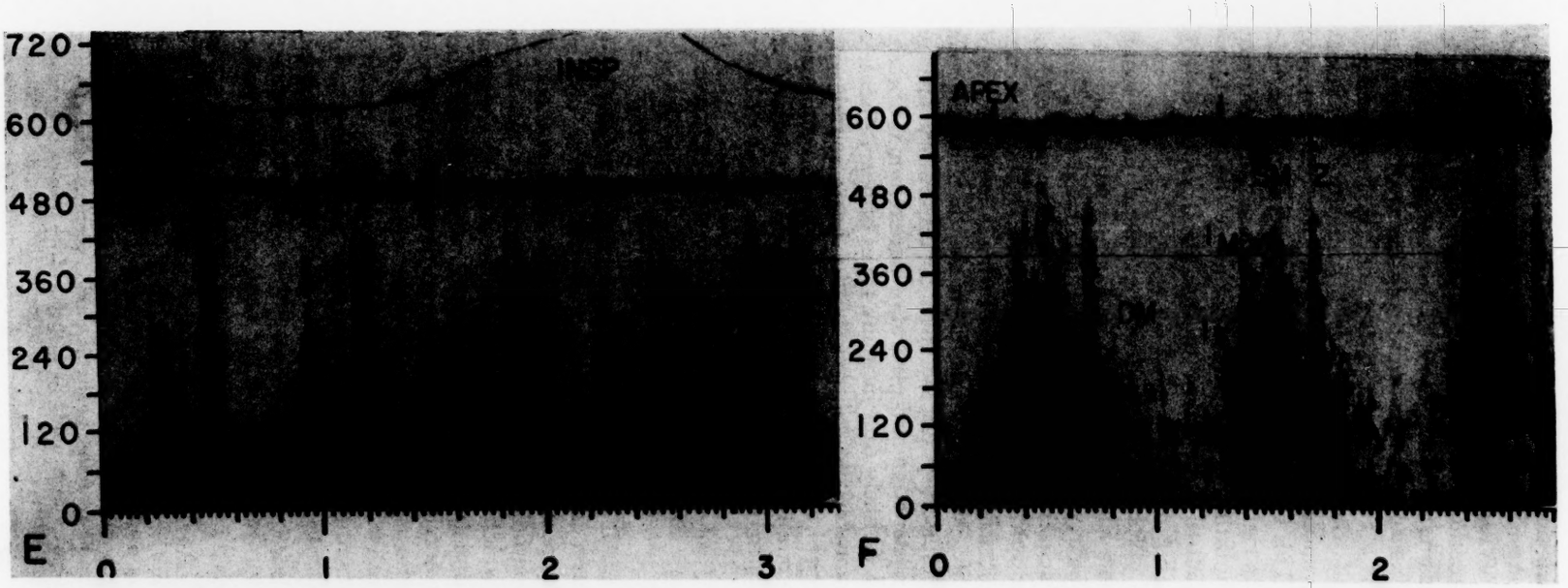

FIG. 2. Mechanical factors in the splitting of heart sounds: A, pulmonary area in thirteen year old child; slight early systolic murmur. B, apex in forty-three year old patient with interatrial septal defect. Each component of split S-2 has frequency pattern of a valve-closure sound. C, pulmonary area in fifty year old patient with systemic arterial hypertension and left-sided thoracoplasty for pulmonary tuberculosis. Split P-2 probably due to exaggerated negativity of intrapleural pressure. Scratchy mid- or late systolic murmur believed to be extracardiac. D, pulmonary area in pulmonary stenosis, probably valvular type; note "Christmas tree" ejection stenosis murmur and delayed pulmonary closure sound or "pulmonary reversal snap" (IIP). The systolic murmur appears to continue slightly after the aortic closure ("IIAO"). E, pulmonary area in twenty year old patient with mitral regurgitation. There is splitting of the second sound which is exaggerated by inspiration; note the decrescendo systolic murmur. F, apex in a patient with rheumatic mitral regurgitation. The systolic murmur begins immediately with the second component of the split first sound which therefore is probably mitral closure sound. If so, it is considerably delayed and has an anomalous relationship to the tricuspid closure sound. The second sound is unitary—presumably only aortic closure sound—and is followed immediately by a decrescendo diastolic murmur which probably had its origin at the aortic orifice.

D. Opening of the arterial valves
E. Ejection vibrations

II. Second heart sound
A. Relaxation of the myocardium
B. Closure of the arterial valves
C. Water-hammer phenomenon in the arteries(?)
D. Opening of the atrioventricular valves

Factors Determining Audibility of Splitting in Heart Sounds. The interval separating the individual components is clearly the most important factor determining audibility of splitting but it is by no means the only factor. It is generally stated that an interval of .05 to .06 second is the minimum detectable by ear. Experience indicates that, when other factors (to be discussed) are favorable, splitting of lesser degrees (of the order of .03 second) can be detected.

The experiments of Helmholtz and of Mayer and Stumpf[14] concerning the greatest number of beats per second that can be heard has relevance in this connection. With pure tones 41 beats per second (interval of about .024 second) are audible at 96 cycles, 58 at 256 cycles (.017 second interval) and 107 at 575 cycles (.009 second interval). For the complex frequency combinations involved in heart sounds, the performance of the ear is much less favorable.

Training and experience are obviously important. When the first of the two split components is unusually accentuated and reverberating, fusion with the second component and reduction in audibility of the splitting results. (An example is the lesser audibility of normal inspiratory splitting of the second sound at the base when the aortic component is greatly accentuated in systemic arterial hypertension.) It is self-evident that splitting will less likely be detected when one of the components is of too low intensity or, what amounts to the same result, is of lower frequency composition than is easily appreciated by ear. Because of the physiologic properties of the ear, a very intense component will render the ear less capable of detecting a second component which would ordinarily be heard and which is separated from the first by an appropriate interval. When the second component is accentuated or when it initiates a murmur, splitting may be more evident.

Splitting of Heart Sounds in Normal Subjects. Splitting of the second sound at the base with inspiration was known a century ago. The classical studies of Potain[15] published in 1862 are particularly noteworthy. Such splitting is usually most striking in children. The normal effects of respiration on splitting provides a useful method for the bedside analysis of splitting in bundle branch block and in conditions simulating split. The normal splitting with inspiration is a result of the discrepancy in stroke volume of the two ventricles. Inspiration increases venous return to the right side of the heart. This is a physiologic counterpart of the increase in right ventricular stroke volume with resultant splitting of S-2 which occurs as a rule with the left-to-right shunt of interatrial septal defect. (Fig. 2A.)

Normal splitting of the second heart sound may be exaggerated in patients with a normal heart who have, however, increased inspiratory negativity of intrathoracic pressure as a result of respiratory disease. (Fig. 2B.) The presence of striking inspiratory splitting in later decades of life, without signs of heart disease, suggests respiratory disease such as inspiratory airway obstruction and pleural or parenchymal fibrosis. It is likely that in many types of heart disease a non-specific splitting of the heart sound with inspiration may result from reduced pulmonary compliance which in turn is secondary to pulmonary congestion or fibrosis.

CLASSIFICATION OF PATHOLOGIC SPLITTING OF HEART SOUNDS AND OF CONDITIONS SIMULATING SPLIT HEART SOUNDS

All true splitting of heart sounds results from asynchrony in closure of the valves on the opposite sides of the heart.* Instances of pathologic splitting fall into two main types which can be called after Leatham[16] electrical and mechanical. In cases of the first type, ventricular asynchronism is the result of delay in the activation of one ventricle relative to the other. Bundle branch block is the classical example and idioventricular pacemaker, as in ventricular premature contractions and complete heart block, another. In the so-called mechanical group the ventricular asynchronism

* Another mechanism for splitting of heart sounds, namely asynchronous closure of individual cusps of a single valve, as proposed by Skoda in 1853,[17] is unlikely as a basis for a significant degree of splitting. No corroboration for this idea could be obtained by examining frame-by-frame available motion pictures of functioning heart valves made at a speed of 24 frames per second. However, the minute splitting of the opening and closing sounds of the Hufnagel valve suggests the occurrence of a similar phenomenon in the heart.[6]

results from a discrepancy in the stroke volumes of the two ventricles as a result of inspiration or shunt or from a discrepancy in the rate of ejection from the two ventricles, as in aortic and mitral regurgitation. A most striking example of splitting of heart sounds of the mechanical type is that seen in the case of the second sound in

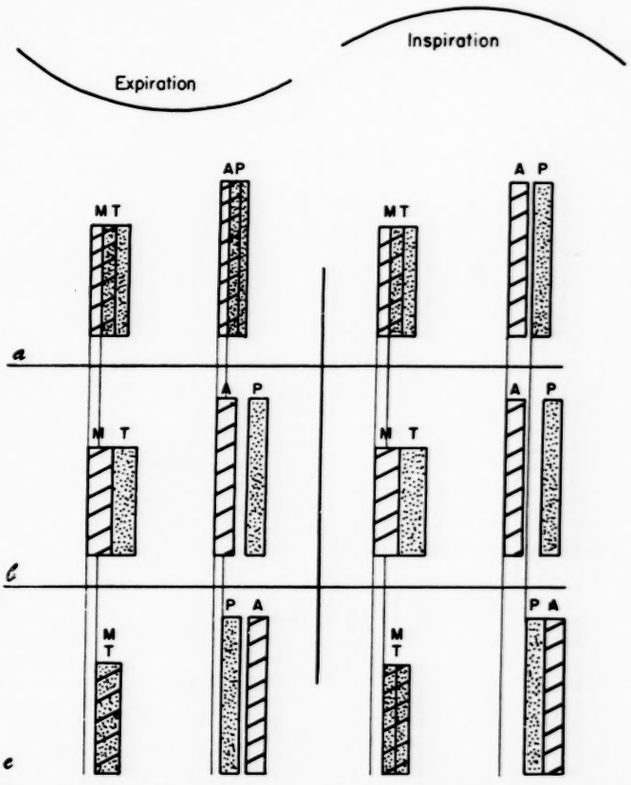

FIG. 3. Effect of respiration on the splitting of heart sounds in bundle branch block: (*a*) normal, (*b*) right bundle branch block and (*c*) left bundle branch block.

atrial septal defect. Here the stroke volume of the right ventricle is increased and the pulmonary closure sound delayed. Seemingly, systole is prolonged in the right ventricle relative to that in the left because of the larger amount of blood with which it is presented. (This is an exaggerated form of the splitting of P-2 which occurs with inspiration in most normal subjects.) The marked inspiratory splitting of the second sound which may occur in patients with an increased negativity phase of intrapleural pressure is another example of "mechanical" splitting.

Those adventitious sounds which may create a situation confused for splitting by the ear and, in some instances, by oscillographic phonocardiography can be classified in this manner:

I. Those confused for split S-1:
   - A. Normal atrial sound
   - B. Presystolic gallop
   - C. Protosystolic click
     1. Due to dilated pulmonary artery
     2. Due to disease of ascending aorta
     3. Due to pericardial adhesions

II. Those confused for split S-2:
   - A. Telesystolic click due to pericardial adhesions
   - B. Mitral opening snap
   - B. Normal third heart sound
   - D. Protodiastolic gallop
   - E. Isodiastolic pericardial snap of constrictive pericarditis.[19,20]

Bundle Branch Block. Ventricular asynchronism and resultant splitting of both heart sounds is to be expected in bundle branch block. In practice, splitting of the second sound occurs more commonly than splitting of the first sound. Furthermore, splitting of impressive proportions is more common in right bundle branch block than in left. Normally the mitral and

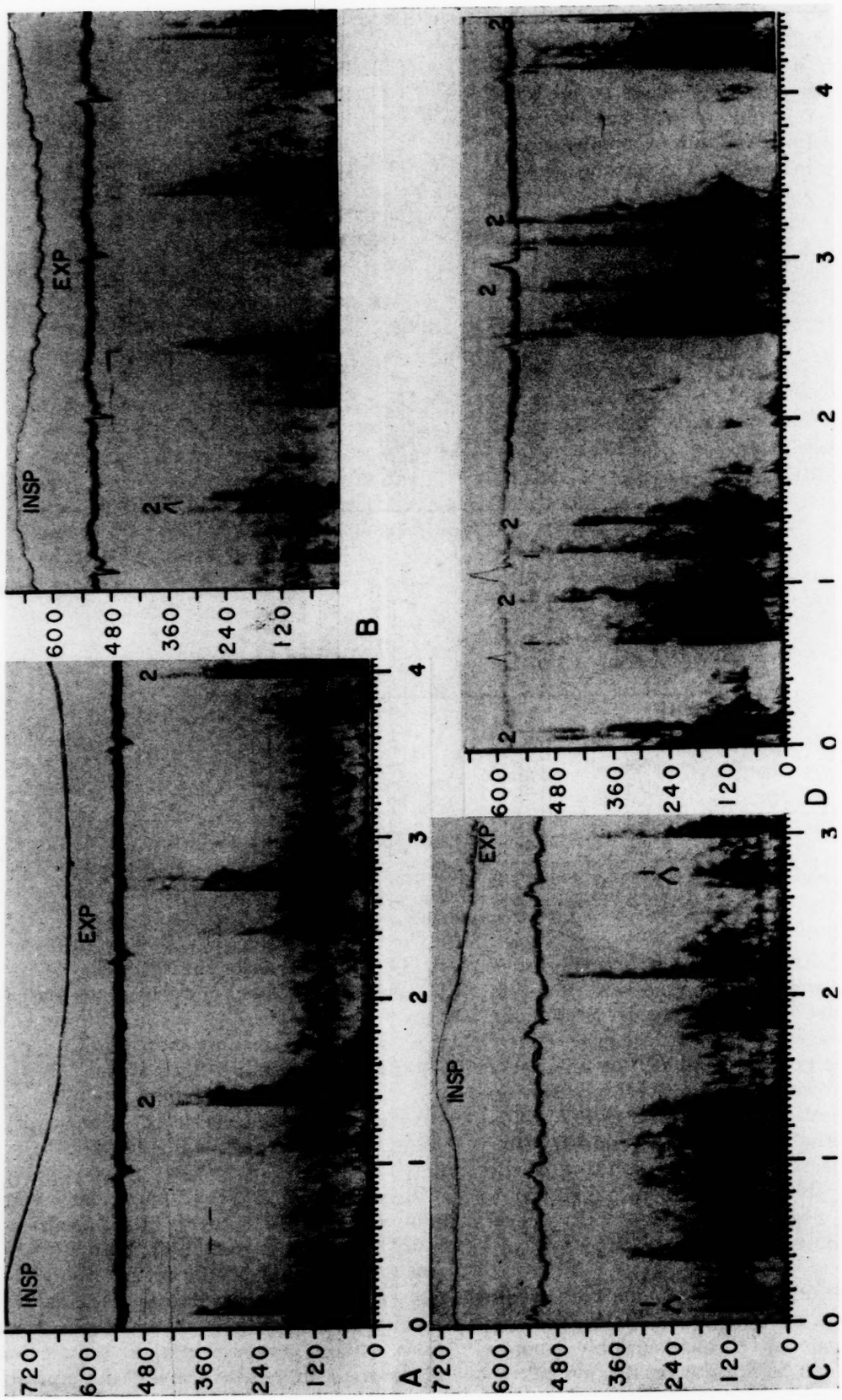

FIG. 4. "Electrical" type of heart sound splitting. A, pulmonary area, left bundle branch block; note paradoxical effect of expiration. B, pulmonary area, right bundle branch block; note exaggeration of splitting with inspiration. C, split first sound in left bundle branch block. Although not clearly split, the second sound is widest in expiration. D, mitral regurgitation; second sound split in normal cycles; both first and second sound split with ventricular premature contractions; note the decrescendo systolic murmur.

aortic closures usually precede slightly the closure of the tricuspid and pulmonary valves. Left bundle branch block is less likely to produce splitting because delay in the closure of the mitral and tricuspid valves tends merely to cancel this normal asynchronism. Right bundle branch block, on the other hand, exaggerates normal asynchronism. It is difficult to understand why the first heart sound (Fig. 4C) is not more frequently and markedly split in cases of bundle branch block than it is, especially since splitting of the first sound does occur quite regularly with ventricular premature contractions, a seemingly comparable situation.

The effect of respiration on the split second sound of bundle branch block is different in the case of the two types, left and right. (Fig. 3.) With inspiration the split is exaggerated in the case of right bundle block and decreased or eliminated in the case of left bundle branch block. These contrasting phenomena are obviously the result of interplay between the normal inspiratory splitting of the second sound and the splitting produced by the bundle branch block. Repeatedly, students informed of these differential points have been able to determine at the bedside the type of bundle branch block present.

When right bundle branch block and a protodiastolic gallop of left ventricular origin are present together, the second component of the second sound can be expected to occur closer to the gallop sound than in the absence of bundle branch block or with left bundle branch block.[18] This is clearly a differential point of less usefulness because of the relative infrequency of the proper combination of sounds and because the split second sound and the gallop tend to have maximum audibility in different areas, pulmonary area and apex, respectively.

These studies have not revealed "three well developed components of the first sound" in bundle branch block as has been said to occur.[18]

Illustrative cases of right bundle branch block are presented in Figures 4B and 5 and of left bundle branch block in Figures 4A and C.

Ventricular Premature Contractions. Although the first heart sound is not commonly split in bundle branch block such splitting does occur as a rule in ventricular premature contractions. This is a bit surprising since they would seem to be comparable situations. Possibly the fact that greater prolongation of the QRS occurs with premature contractions than with bundle branch

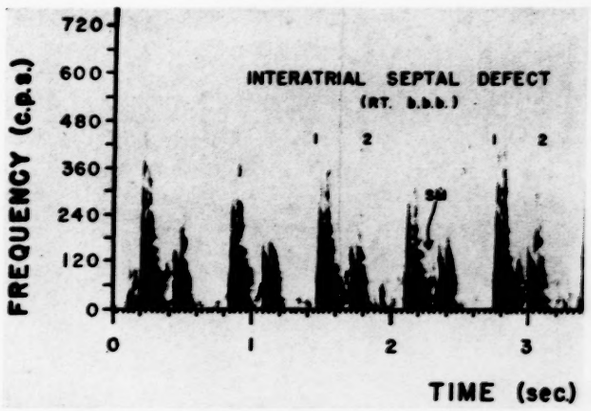

FIG. 5. Splitting of both the first and the second heart sounds in a patient with two mechanisms for splitting: right bundle branch block and interatrial septal defect.

block accounts for the seemingly conflicting results. Occasionally it is possible to localize the initiating focus to one or the other ventricle by comparing the intensity of the two components of each sound in the several areas. Figure 4D demonstrates splitting of both the heart sounds produced by a ventricular premature contraction. The patient also had rheumatic mitral regurgitation and it is of note that the second heart sound is split in normal cycles. This type of splitting is to be discussed in more detail later.

Shunts, Particularly Interatrial Septal Defect. Splitting of the second sound occurs in the great majority of cases of interatrial septal defect. (Fig. 1B.) This splitting appears to be the result of the discrepancy in stroke volume of the two ventricles. This is a situation comparable to the splitting of the second sound which occurs normally with inspiration and which is also the result of discrepancy in ventricular stroke volumes. When right bundle branch block is also present, the splitting is exaggerated. (Fig. 5.) Respiration has little or no influence on the splitting of the second sound in these cases.

In about half the patients with interatrial defect splitting of the first sound is also present. The splitting of the first sound must have a different basis than the splitting of the second sound. Prolongation of iso(volu)metric contraction cannot be the basis since by definition both the arterial and the atrioventricular valves are closed during this phase. It is possible that a delay in the tricuspid closure results from the fact that right up to the time the dilated right ventricle contracts it is still accepting blood and the tricuspid leaflets are spread to a maximum

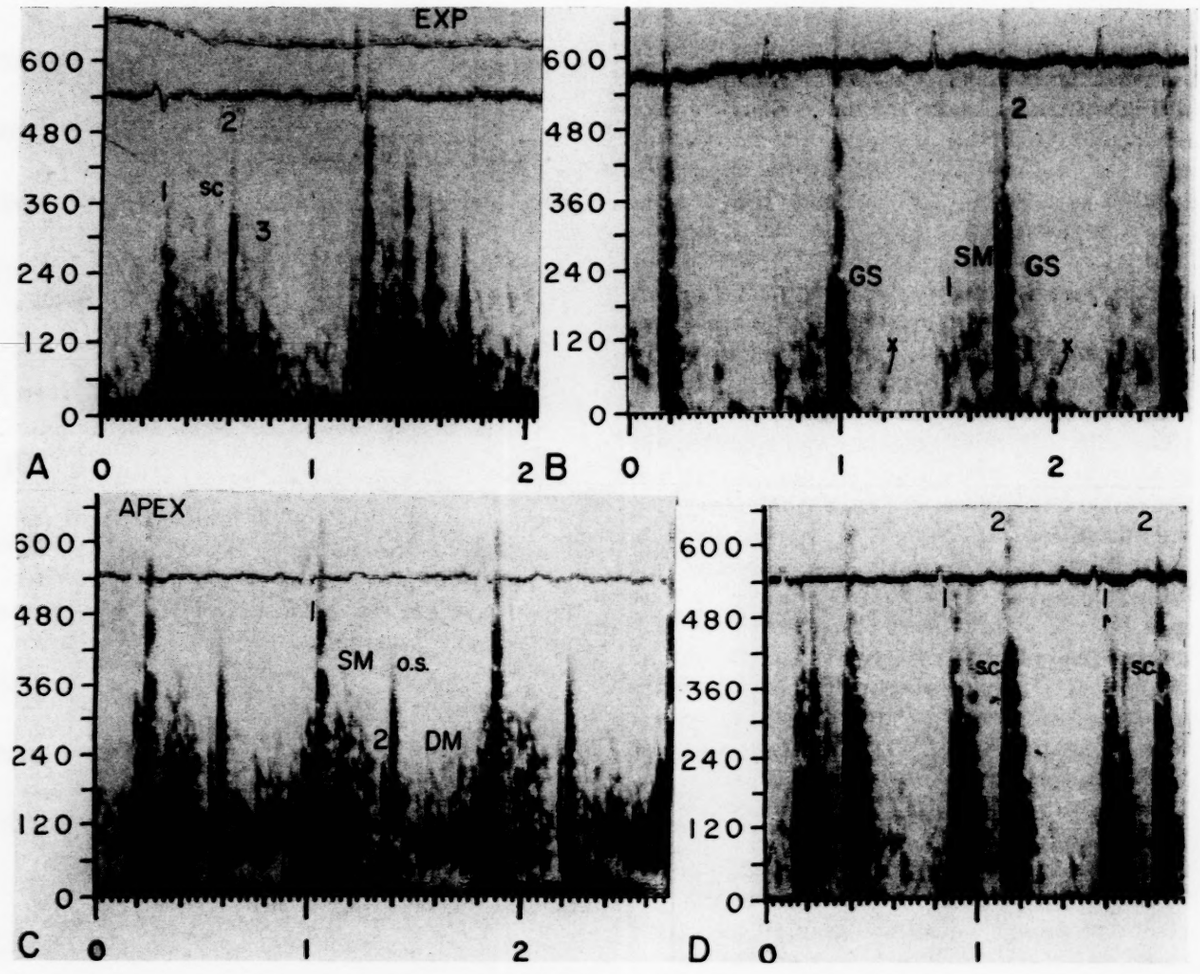

FIG. 6. Phenomena simulating split sounds. A, late systolic click of about the same intensity as seen at the apex was also present at left sternal border and pulmonary area. There is a history of acute rheumatic fever, during which pericarditis was observed, four months before this recording; third heart sound is also present. B, this patient with mitral stenosis had considerable pulmonary hypertension with resultant accentuation of the pulmonary closure sound. The temporal relationship of the two components of P-2 is not altered. There is an exceedingly subtle diastolic murmur (probably Graham Steell) beginning immediately with P-2. There is a faint sound in mid-diastolic (which is difficult to identify) at the termination of the Graham Steell murmur. It is too early for an atrial heart sound and perhaps too late for a third heart sound. It may represent a valve closure sound—slight leak occurs through a small separation of the cusps as long as the pressure differential is sufficient to maintain the separation. As soon as the pressure differential drops below a certain threshold, coaptation of the previously separated surfaces occurs with production of an audible sound. C, recording at the apex in a patient with severe mitral stenosis and a moderate degree of mitral regurgitation; note the snapping mitral closure sound, the systolic murmur and the diastolic murmur with presystolic crescendo. There is seemingly a split second sound. Actually it is clear that this is in fact a second sound followed closely by an opening snap. This patient also has aortic stenosis. The aortic closure sound is so attenuated that it is doubtful that it is transmitted to the apex where the pulmonary closure sound alone is represented. That the sound marked OS is indeed mitral opening snap is corroborated by its snapping appearance, pure frequency content and elevated frequency "bottom." D, an example of early systolic sound in the pulmonary area caused by dilated pulmonary artery due in this case to atrial septal defect. In addition both the first and the second sounds are slightly split.

degree. The left ventricle, on the other hand, because of its different pressure-volume characteristics will more likely have completed filling at the corresponding time and the mitral valve will be partially closed.

Since many cases of interatrial defect have an early systolic click on the basis of dilated pulmonary artery, this must be distinguished from splitting of the first heart sound.

Anomalous pulmonary venous return can be

expected to produce a splitting of heart sounds of the same type as that which occurs in interatrial defect. Our experience with spectral phonocardiography in this anomaly is limited. Patent ductus arteriosus, by increasing the stroke volume of the left ventricle over that of the right, should produce splitting of heart sounds. That splitting does not occur more commonly with patent ductus may be yet another instance of absent splitting with delay in the left-sided valvular events.

Variations in Arterial Pressure. It is the general impression that hypertension causes splitting of the second heart sound, and especially that pulmonary hypertension causes a split P-2. Phonocardiographic analysis does not corroborate this impression. Even clinical experience does not relate splitting of the second sound to systemic arterial hypertension. In pulmonary hypertension studies, very slight splitting was frequently demonstrated. However, the temporal relationship of aortic and pulmonary closure was not altered: pulmonary closure did not occur prematurely as a result of elevation of pulmonary arterial pressure. (Fig. 6B.) The pulmonary closure sound was, of course, accentuated in intensity and frequency span. With pronounced elevation of pulmonary pressure the sound was often prolonged and reverberating. The clinical impression of split P-2 with pulmonary hypertension has been engendered in large part by the easy audibility of the mitral opening snap in the pulmonary area of patients with pulmonary hypertension on the basis of mitral stenosis.

Contrariwise, hypotension in the pulmonary artery in congenital pulmonary stenosis can result in delay of pulmonary valve closure and splitting of the second sound. (Fig. 2D.) Since it is the pressure differential on the two sides of the valve that controls its closure, the effect of pulmonary hypotension is relatively greater by reason of the ventricular hypertension. When ventricular systolic pressure is in the range of 300 mm. Hg or even higher, it might be anticipated that a longer time will be taken for this pressure to fall below that in the pulmonary artery.

In cases of valvular pulmonary stenosis of the congenital type, the valve is as a rule merely a perforated membrane. Valve closure in the usual sense is inconceivable. The sound that is heard and recorded is probably a snap of this diaphragm toward the ventricle. This sound may be termed "pulmonary reversal snap."

A rough indication of the pulmonary pressure in cases of tetralogy of Fallot with infundibular stenosis can be obtained from the presence or absence of a pulmonary closure sound. Furthermore, after an adequate Blalock-Taussig operation, the pulmonary closure sound should become evident in such cases, providing pulmonary atresia is not present.

Valvular Heart Disease. Delay of the mitral closure sound is characteristic of mitral stenosis especially if atrial fibrillation is also present. (Fig. 1B.) This delay may be due largely to the elevation of left atrial pressure since the delay is greatest in cases with the greatest elevation of left atrial pressure. Splitting of the first sound is not more common in mitral stenosis than it is, due to the usual precedence of mitral closure over tricuspid closure and to obscuration of the tricuspid closure sound by the presystolic rumble in cases with sinus rhythm. (Fig. 6C.)

In mitral regurgitation splitting of the first sound of the same type, delay in mitral closure, is not infrequently demonstrable and the systolic murmur is found to begin immediately with the second component, the mitral closure sound. (Fig. 2F.)

Splitting of the second heart sound occurs commonly in severe mitral regurgitation. (Figs. 2E and 4D.) Presumably because of the double route of ejection from the left ventricle, aortic closure occurs prematurely. This splitting is likely to be obscured, however, by the systolic murmur and may be demonstrable only by graphic methods. Because of low diastolic pressure in the aorta and accelerated left ventricular ejection, S-2 may be split in aortic regurgitation.

Absent Pericardium. In our experience, splitting of the heart sounds is a frequent finding in patients in whom the pericardium has been removed for relief of constrictive pericarditis or for other reasons.

Clicks and Snaps. Early or late systolic clicks produce a situation easily confused with split first or second sound, respectively. The opening mitral snap (Fig. 6C) is equally easily confused with the second component of a split second sound. The genesis and clinical significance of systolic clicks are discussed in more detail elsewhere.[3,21] The most frequent cause of early systolic click is disease with dilatation of the ascending aorta or the pulmonary artery.

Pericardial adhesions may be responsible for telesystolic clicks as well as some protosystolic ones. The ear can often distinguish systolic clicks and opening snaps from valve sounds by their snapping quality. Similarly, the spectral phonocardiogram usually displays distinctive features in these added sounds: they usually have more homogeneous frequency content and often their "frequency bottom" is not at the baseline, as in the case of valve sounds. The presence of demonstrable splitting of heart sounds proper, in addition to the added sound, clinches identification of the click or snap on auscultation and in the spectral phonocardiogram. See Figures 6A, C and D for examples of clicks and snaps which create combinations of sounds simulating splitting.

Gallops. In gallops the degree of separation of the added sound from the heart sounds proper endows the rhythm with a cadence rarely encountered with true splitting of the heart sounds. When any question arises the relationship to the electrocardiogram will, in the case of the atrial gallop which precedes the QRS, identify the adventitious sound. Possibly more easily confused with a split second sound is the early diastolic sound, sometimes termed gallop, noted in constrictive pericarditis and also pericarditis with effusion.[19,20] This sound occurs closer to the second sound than does the protodiastolic gallop. (Fig. 6A.) "Isodiastolic pericardial snap" is Lian's term.

SUMMARY AND CONCLUSIONS

Normal and pathologic conditions resulting in splitting of heart sounds are reviewed. The influence of respiration on splitting of the second sound can assist in identifying the type of bundle branch block present and in distinguishing true splitting of heart sounds from simulating conditions. Arterial hypertension is not a cause of splitting of heart sounds. Asynchronism of valve closures is the fundamental basis for splitting of heart sounds and may have two general bases which, following the terminology of Leatham,[16] may be designated electrical (asynchronism due to abnormality in the activation of the ventricles, as in bundle branch block, ventricular extrasystoles and idioventricular rhythm) and mechanical (asynchronism due to discrepancy in ventricular stroke volumes, as in atrial septal defect, or in rate of ejection, as in mitral and aortic regurgitation). In a patient over forty years of age without other evidence of heart disease, striking inspiratory splitting of heart sounds suggests respiratory disease which is accompanied by exaggeration of intrapleural negativity of pressure during inspiration. Inspiratory airway obstruction as by bronchogenic carcinoma or asthma and parenchymal or pleural fibrosis are possibilities.

Early and late systolic clicks and the mitral opening snap are the conditions most likely to simulate splitting of heart sounds.

Because of much overlap of the degree of splitting with that occurring normally, splitting is of limited diagnostic value in the pathologic states with which it may occur: interatrial septal defect, bundle branch block, mitral or aortic regurgitation and respiratory disease resulting in exaggerated cyclical variations in intrapleural pressure. In general, however, splitting has more pathologic significance (1) when it occurs in adults than when it occurs in children, (2) when splitting is exaggerated with expiration rather than with inspiration (left bundle branch block), (3) when there is no clinical evidence of respiratory disease and labored respirations and (4) when splitting persists throughout all phases of respiration (as usually is the case in interatrial septal defect).

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Diagnostic Value of Phonocardiography in Mitral Stenosis*

Mode of Production of First Heart Sound

J. J. KELLY, JR., M.D.
Brooklyn, New York

IN 1911 Weiss and Joachim[1] reported a delay in the onset of the first heart sound in mitral stenosis. More than thirty years later Cossio and Berconsky[2] rediscovered this phenomenon using a more refined technic of phonocardiography. In 1951 Sprague and his associates,[3] unaware of either publication, reported a similar study, again demonstrating that in subjects with mitral stenosis and atrial fibrillation the interval between QRS of the electrocardiogram and the first heart sound varied inversely with the length of the previous cycle. This was confirmed by Wells in England.[4]

In the present study further information was sought concerning the range of the Q-first heart sound interval in mitral stenosis and in other forms of heart disease. As in the other studies, measurements were made in simultaneously recorded electrocardiograms and phonocardiograms. The Q-first heart sound interval is the time from the beginning of ventricular excitation (Q wave or onset of upstroke of R wave in limb Lead II) to the first rapid vibrations of the first heart sound. Hereinafter this interval will be referred to as the Q-1 interval. The records of subjects with a QRS duration of .11 second or more were excluded from this study because bundle branch block in itself may cause an apparent delay in the first heart sound.[5,6] Sounds associated with extrasystoles were omitted for the same reason.[7,8]

The phonocardiograms were taken either with a Cambridge Simplitrol or a Sanborn Twin Beam phonocardiograph. The paper speeds on the respective machines were 50 and 75 cm. per second, allowing one to measure with an accuracy of .01 second. The measurements by independent examiners of records were always within .01 per second. Ten intervals of each subject were measured and averaged. The subjects were resting in the supine position when the records were obtained. Phonocardiograms were routinely taken at the apex, Erb's point, the pulmonic and aortic valve areas but measurements were made from the apex recordings.

RESULTS

In a group of a hundred patients with cardiac lesions of all types except those involving the mitral valve the mean Q-1 interval was found to be .04 second with a standard deviation of .01 second. Values of normal man compiled from different sources by Wiggers[9] are in close agreement with these figures.

In a group of seventy-five subjects with mitral stenosis as the only lesion, the mean Q-1 interval was .06 second with a standard deviation of $\pm$.03 second.

These data are presented as frequency distribution graphs in Figure 1. Inspection of these charts demonstrates a wide spread of the Q-1 interval in the mitral stenosis group, ranging from .04 to .10 second. But more striking is the fact that 45 per cent of the values are .07 second or greater whereas in the group of subjects with normal mitral leaflets no intervals of .07 second or greater can be seen.

In subjects with mitral stenosis and atrial fibrillation the length of the Q-1 interval was found to vary inversely with the length of the previous diastole, as reported earlier.[2-4] No such variation was found in patients who had atrial fibrillation but who did not have mitral stenosis. In this latter group no significant

* From the Department of Medicine, State University of New York, College of Medicine at New York City, and the Kings County Hospital Center, Brooklyn, New York. This work was supported in part by a grant from the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health.

difference was found between those subjects with sinus rhythm and those with atrial fibrillation. In the mitral group the length of the Q-1 interval paralleled the severity of the stenosis. Age seemed to be the factor determining rhythm. In this population atrial fibrillation was uncommon before the age of forty unless active carditis was present.

TABLE I

Patient	Q to First Sound (seconds)		Second Sound to Opening Snap (seconds)	
	Pre-operative	Post-operative	Pre-operative	Post-operative
1	0.10	0.07	?*	0.04
2	0.07	0.05	0.05	0.08
3	0.08	0.04	0.04	0.07
4	0.08	0.05	0.05	0.08
5	0.07	0.05	0.06	0.08
6	0.08	0.06	0.06	0.11
7	0.08	0.05	0.07	0.10
8	0.06	0.04	0.06	0.09
9	0.08	0.05	0.04	0.08
10	0.07	0.05	0.05	0.08
11	0.09	0.06	?*	0.05
12	0.06	0.04	0.06	0.10
13	0.08	0.08	0.05	0.05
14	0.07	0.05	0.06	0.09
15	0.06	0.05	0.04	0.08
16	0.07	0.04	0.08	0.12

* Opening snap not identified on phonocardiogram.

Twenty-seven persons with mitral insufficiency were also studied. A mean Q-1 interval of .04 second with a standard deviation within ±.01 second was found, a normal value in agreement with the observations of Brigden and Leatham.[10]

A delay in the interval from the beginning of the QRS to the most intense portion of the first sound was also demonstrated in mitral stenosis, in the presence of which the mean was found to be .09 second (standard deviation = ±.03) whereas in mitral insufficiency the mean was .05 (standard deviation = ±.01) and in the control group .05 (standard deviation = ±.01) second.

Although this investigation was designed primarily to show the variation in the Q-1 interval, a record was also made of the frequency of occurrence of the opening snap of the mitral valve. The opening snap of the mitral valve was the term given by Rouches[11] in 1888 to a high pitched sound of short duration which closely follows the second sound by which is of maximal loudness just inside the apex rather than at the base, as would be the case with a split second sound. This sound was recognized as early as

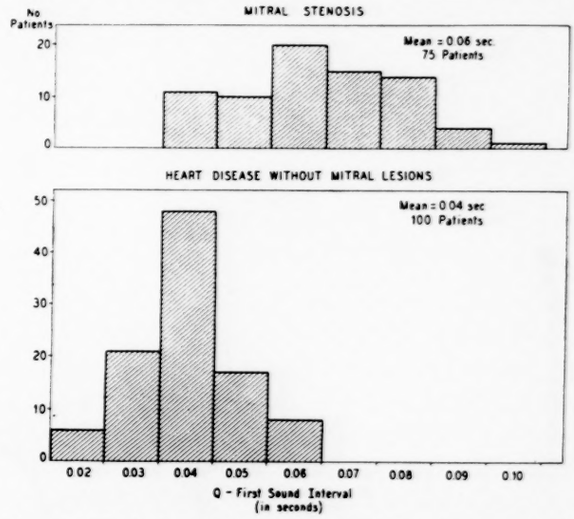


FIG. 1. Variation of the interval from the onset of electrical activation of the ventricles to the first rapid vibrations of the first sound as seen in the simultaneously recorded lead II of the electrocardiogram and the apical phonocardiogram. Subjects with QRS times 0.11 second or greater were excluded.

1835[12] as a frequent accompaniment of mitral stenosis but was labelled an apical split second sound.

An opening snap was found on phonocardiography in seventy-two of the seventy-five subjects who had mitral stenosis but in only one patient who did not have significant mitral stenosis; this occurred in a patient whose condition was diagnosed as mitral stenosis but it was found at operation that only one cusp with its chordae tendineae became fibrotic. This produced a moderate insufficiency but no appreciable stenosis. A similar high incidence of the opening snap in mitral stenosis has been reported recently by Mounsey[13] who recorded it in thirty-two of thirty-three patients with mitral stenosis. This sound, it should be pointed out, is commonly confused with a gallop or a split second sound.

The presence of an opening snap is of great diagnostic significance. It is a more frequent finding in severe mitral stenosis than is a diastolic murmur. We were unable to hear or record a diastolic murmur in seventeen patients with mitral stenosis yet in fourteen of these an opening snap was recorded.

The data from preoperative and postoperative tracings in sixteen patients who underwent mitral valve fracture are presented in Table 1. In every instance except one a shortening of the Q-1 interval followed surgery. (The one patient who was the exception derived no benefit from the operation.) Also, the interval from the beginning of the second sound to the opening snap of the mitral valve lengthened with surgery. This latter interval (O-S interval) apparently varies with isometric relaxation of the left ventricle. No change in the left ventricular volume occurs during this interval but when the pressure in the left ventricle falls below that in the left atrium the mitral valve snaps down and filling of the ventricle begins. When there is no change in the systemic arterial pressure a lengthening of the isometric relaxation time (O-S interval) can be interpreted as the result of reduction of the left atrial pressure following mitral valvotomy.

DISCUSSION

The observations reported here clearly demonstrate the frequency of prolonged Q-1 intervals in mitral stenosis and the absence of such delay with cardiac lesions of other types. In any subject with a Q-1 interval of 0.07 second or greater (in the absence of bundle branch block), it may be taken for granted that there is a significant degree of mitral stenosis. This knowledge may have considerable clinical usefulness. As an example, in a patient with unexplained heart failure no murmurs were heard at first. The usual laboratory investigations such as electrocardiography and fluoroscopy revealed only atrial fibrillation and enlargement of all chambers of the heart. Mitral stenosis was strongly suspected because the Q-1 interval was 0.10 second. Later, when the heart failure was better controlled, a diastolic rumble was heard and recorded at the apex. At operation a very tight mitral valve orifice was found.

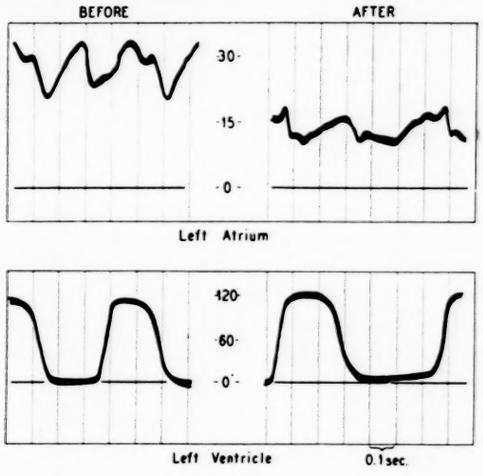
In a clinic such as ours where the end stages of disease are commonly seen, mitral stenosis without murmurs is frequently encountered. When the cardiac output falls to very low values the typical mitral rumble frequently disappears. If the mitral valve is extensively calcified the first sound often loses its usual loud snapping quality and the opening snap may be absent.[14] It is under these circumstances that the delay of the first heart sound is of real help in establishing the diagnosis; in several of these cases preoperative confirmation was provided by demonstrating calcified valves in slit kymograms.

Mid-diastolic murmurs are quite common in congenital heart disease.[15] The presence of such murmurs invariably arouses speculation concerning the presence of mitral stenosis. If no ventricular conduction defect is present and the first heart sound is delayed, it will be found that mitral stenosis also is present. Also, an Austin Flint murmur may be definitely excluded in a patient who has aortic insufficiency and a presystolic murmur if a delay in the onset of the apical first sound is found.

The mechanism by which the first sound is delayed in mitral stenosis can be explained readily by the hypothesis[16,17] that the first heart sound is caused by sudden tensing of the auriculoventricular valves and chordae tendineae when the auriculoventricular septum is pushed in the direction of the auricle. In mitral stenosis the left atrial pressure is high while the end diastolic pressure in the left ventricle is low. The mitral valve does not close until the left ventricular pressure exceeds that of the left atrium. This disparity of pressures in the atrium and ventricle is found consistently in mitral stenosis.[18,19] This is illustrated in Figure 2 which demonstrates pressures obtained in the operating room from both the left atrium and the left ventricle before and after mitral fracture.

In Figure 3 are presented data from the same patient. Here ventricular pressures were recorded at a greater sensitivity of the strain gauge so that the atrial curves could be traced over the segments of the ventricular pressure curves. Also indicated in this illustration is the position in time of the first heart sound, second sound and the opening snap as recorded preoperatively and postoperatively. Although the ventricular end diastolic pressure and the electrical mechanical interval remained constant before and after surgery, the time required by the ventricle to develop pressure greater than that in the left atrium fell from 0.08 second to 0.05 second after enlargement of the mitral orifice. These time periods agree perfectly with the Q-1 intervals determined phonocardiographically pre- and postoperatively. It is also apparent that a significant degree of mitral stenosis remained after surgery, as indicated by a difference of 10 mm. Hg between the end diastolic pressures in the atrium and the ventricle. When these pressures are equal the onset of the first sound begins with ventricular contraction. In left

ventricular failure and in constrictive pericarditis left atrial pressure is also elevated but there is no impediment to ventricular filling as in mitral stenosis, and in these instances the end diastolic pressures are equal in the left atrium and ventricle. Hence no delay would be expected in the onset of the first sound and none has been observed.



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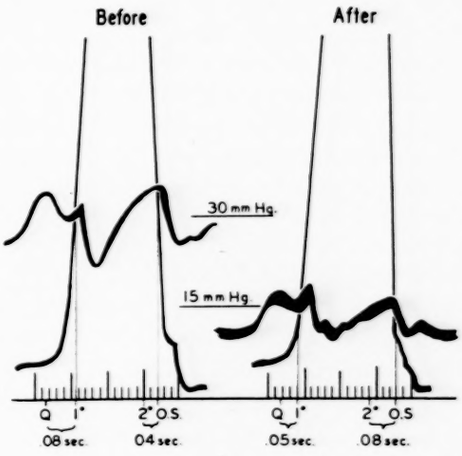

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FIG. 2. Left atrial and ventricular pressures recorded by needle puncture of these chambers before and after mitral valvuloplasty.

FIG. 3. Mitral valvuloplasty. Pressures from the same patient as in Figure 2 but in this instance the ventricular pressures were recorded at a greater sensitivity of the strain gauge so that the atrial curve could be superimposed on the ventricular curve. Q refers to the onset of the QRS complex of the electrocardiogram; 1° refers to the first sound, 2° to the second sound and O.S. to the opening snap. Phonocardiograms were taken preoperatively and postoperatively (the heart rates at these times were the same). The electrical-mechanical interval of the left ventricle remained constant at 0.03 second.

It is also of interest that in subjects with significant mitral insufficiency the Q-1 interval is normal. Apical systolic murmurs, which are not uncommon in mitral stenosis, do not necessarily indicate any serious degree of mitral insufficiency. A recent experience vividly brought this lesson home to us. A middle-aged woman who was studied in our laboratory was found to have a normal QRS time, a loud first sound, a grade IV pansystolic apical murmur and an opening snap which was recorded but not heard by most examiners. Because the first sound was loud and delayed (Q-1 $\pm$0.09 second) it was predicted that a severe degree of mitral stenosis was present and that mitral insufficiency would be minimal in spite of the intense murmur. This prediction was confirmed by postmortem examination a week later when a very rigid, tightly stenotic valve was found. The cusps of this valve could not possibly close completely during systole. However, when the mitral valves are severely incompetent, as much blood may be injected into the atrium as into the aorta. In instances such as this the first sound is faint or lost in the systolic murmur but its onset is never delayed. A gallop, which is rare in mitral stenosis even when complicated by right ventricular failure, may be the loudest sound heard in severe mitral insufficiency and has been confused with the first sound. Such gallops occur 0.10 to 0.18 second after the second sound and therefore are not easily confused with opening snaps occurring between 0.02 and 0.13 second after the second sound. For an excellent discussion of mitral insufficiency the paper of Brigden and Leatham[10] should be consulted.

A long Q-1 interval and a short O-S interval are characteristic of tight mitral stenosis. Using the surgeon's estimate of the mitral orifice at operation, Wells[4] demonstrated a better correlation of the size of the mitral orifice with a consideration of both the Q-1 and O-S intervals together than when considering either separately. By subtracting the O-S interval from the Q-1 interval values greater than minus 0.01 second were found with severe mitral stenosis. If the values gave more negative results than minus 0.015 second, an orifice greater than 1 sq. cm. could be expected.

Our experience in general confirms Wells'

views but there are rare exceptions and diagnostic pitfalls which should be briefly discussed. Figure 1 demonstrated that only 45 per cent of the subjects who had mitral stenosis had a Q-1 interval outside the range of the control group, which varied between 0.02 to 0.06 second. Presumably, most of the patients whose Q-1 interval fell within the normal range had only a moderate or minimal degree of mitral stenosis. However, in rare instances we have found that subjects with normal Q-1 intervals may have tight mitral stenosis at necropsy. The explanation for this apparent discrepancy may be found in a very short electrical-mechanical interval of the left ventricle: that is, the time between the electrical activation of the ventricle (Q wave or upstroke of R wave of the electrocardiogram) to the onset of the left ventricular pressure rise. In those persons in whom the heart does not have ventricular conduction defects this time varies between 0.02 second and 0.06 second with a mean of 0.04 second,[19] which is the mean of the Q-1 interval in the group of patients who do not have mitral stenosis.

If a patient with severe mitral stenosis had a left ventricular electrical-mechanical interval of 0.02 second, and 0.03 second further elapsed before the ventricle could develop pressure necessary to exceed the left atrial pressure so that the mitral cusps could snap shut, then the Q-1 would be the sum of these two values, or 0.05 second, which is within the normal range.

Although the electrical-mechanical intervals were determined by needle puncture of the ventricle at operation, this same information may be obtained by the simple, non-hazardous method of recording the apex impulse. The onset of the systolic deflection of the apex beat coincides perfectly with the ventricular pressure rise determined directly. This technic was utilized by Cossio[20] to support the valvular theory of the first heart sound. In patients with mitral stenosis he was able to record the usual apex motion occurring without delay, followed by a sharp apical shock synchronous with the delayed first heart sound.

Another factor affecting the Q-1 interval in mitral stenosis is the rate of rise of ventricular pressure. In twelve instances in which left ventricular pressure curves were obtained the rate of pressure rise varied between 4 mm. Hg and 14 mm. Hg per 0.01 second. Preliminary studies of our data suggest that the rate of rise is much slower in patients with extensive myocarditis, whether active or healed.

In one instance we mistakenly made the diagnosis of mitral stenosis by confusing as the first sound a loud, early systolic sound which was of maximal intensity at the pulmonic area rather than at the apex. Such sounds are usually associated with pulmonary artery dilatation and pulmonary hypertension.[21] This particular patient had a ruptured aortic cusp which produced a continuous murmur from the second sound to the "early systolic click," with no recognizable first sound. To avoid this type of error it is wise to compare the intensity of the first sound both at the apex and at the base of the heart. When a dilated aorta or, more commonly, a dilated pulmonary artery is present a sound is emitted as the semilunar valves open or shortly thereafter. Usually no sound can be detected by the phonocardiogram when the semilunar valves open; however, with dilatation of either of these major vessels the sound may be as loud as that arising from the auriculoventricular valves.

The observations reported herein provide valid evidence that ventricular muscular contraction contributes no audible element to the first sound. In extreme cases the first sound may not begin until 0.06 second after ventricular contraction occurs. It also appears that in mitral stenosis the first heart sound is caused by the tensing of the mitral valve and its chordae; the tricuspid valve contributes no easily audible portion when the delay is great, otherwise a split first sound rather than a delayed sound would be recorded. For example, in a patient with a Q-1 interval of 0.09 second the right ventricular pressure exceeded the right atrial pressure 0.04 second after the Q wave of the electrocardiogram, yet no sound could be recorded at that moment even close to the sternum. Rarely has it been possible to demonstrate by great amplification of the phonocardiograph a faint sound synchronous with closure of the tricuspid valve in instances of mitral stenosis with an intense and delayed first sound.

This situation may be similar to that in left ventricular failure with severe systemic arterial hypertension. In patients with such conditions there is often a very faint first sound but after correction of the failure and reduction in the residual volume in the left ventricle the first sound becomes more intense. Presumably, in failure with an increase in residual volume and

rapid ventricular filling the valve leaflets are approximated at the end of diastole, whereas in healthy persons they may be deep in the ventricle when systole begins and sudden tensing causes a much louder sound. This can be illustrated with a handkerchief producing a faint or loud sound depending on the slackness of the cloth before it is snapped taut.

Perhaps the tricuspid valve normally causes little sound because of physical differences from the mitral valve. In our experience with patients who have pure right ventricular failure gallop is often absent, never more than barely audible, in contrast to gallop in left heart failure which usually is easily audible. However, inaudible vibrations related to gallop phenomena are usually recorded by ballistocardiography and roentgenkymography in patients with right ventricular failure.[22] It is also of interest that Thayer,[23] in his classic paper on the third heart sound, stated that he could easily hear a third sound over the exposed left ventricle of a dog but not over the right ventricle. We have had the opportunity of studying a woman with cor pulmonale and right thoracoplasty whose heart beat directly against the subcutis to the right of the sternum. It was possible to record a presystolic gallop directly over the right atrium, although the gallop was inaudible elsewhere over areas with the usual chest structures intact. This too suggests that normally the tricuspid sound may be faint and poorly transmitted to the precordium. Rytand[24] concluded from another type of study that the first heart sound is largely of mitral rather than of tricuspid origin in normal persons and in patients without mitral stenosis.

The theory of the valvular origin of the first sound explains such common clinical phenomena as the variation in intensity of the first sound in complete heart block[24,25] with varying P-R intervals,[25,26] auricular fibrillation[27] and ventricular tachycardia.[17] The theory of the muscular origin of the first sound cannot explain an intense first sound heard with a ventricular extrasystole which fails to develop enough ventricular pressure to open the semilunar valves or a faint first sound in aortic insufficiency in which the stroke volume may be tremendous. All of these observations are explained neatly by the valvular origin of the first sound. With intense first sounds the auriculoventricular valves are deep in the ventricle and the chordae tendineae are slack when ventricular contraction begins; with faint first sounds the valves are closely approximated at this time. Mitral stenosis or the presence of a short P-R interval should be suspected, therefore, when a loud first sound is heard in a patient with congestive failure.

The lengthening of the interval from the second sound to the opening snap of the mitral valve following mitral surgery has been demonstrated. Figure 3 easily explains this phenomenon. It can be appreciated from this illustration that three variables affect the length of this interval. They are: (1) the height of pressure in the ventricle at the end of systole, (2) the speed of isometric relaxation and (3) the height of the atrial pressure. With reduction of atrial pressure after surgery and with no change in the other variables a lengthening of this interval occurs. In such instances there was no change in ventricular pressure or speed of isometric relaxation, and the O-S interval increased from 0.05 second preoperatively to 0.08 second postoperatively. These observations confirm the views of Margolies and Wolferth[28] expressed in their classic paper on the importance and the mechanism of production of the opening snap in mitral stenosis.

SUMMARY

1. The time of onset of the first heart sound is related to the simultaneous electrocardiogram in subjects with mitral stenosis, mitral insufficiency and heart disease without mitral valve disease.

2. A delay in the first heart sound occurred in patients who had mitral stenosis but who had no other lesions if ventricular conduction defects were absent. The degree of delay paralleled the severity of the mitral stenosis. This delay of the first heart sound has proved to be of diagnostic value, particularly since it is usually greatest when the typical murmurs are absent. No delays occur with significant mitral insufficiency.

3. Significant shortening of the Q-first sound interval occurs with successful enlargement of the mitral orifice.

4. The delay of the first sound can be explained by the disparity between the end diastolic pressures in the left atrium and left ventricle. The sound does not occur until ventricular pressure equals or exceeds atrial pressure.

5. Ventricular contraction does not contribute to the audible portion of the first sound.

Moreover, this sound probably arises chiefly in the mitral rather than in the tricuspid valve.

6. The length of the interval between the second sound and the opening snap of the mitral valve is, in general, inversely related to the severity of the mitral stenosis. This interval lengthens with successful mitral surgery.

7. The mechanism of production of the opening snap is discussed and observations offered which confirm the views of Margolies and Wolferth[28] concerning this phenomenon.

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The Triad of Tachycardia, Digitalis Toxicity and Mercurial-fast Edema in Congestive Heart Failure Complicated by Pulmonary Embolism

WILLIAM R. TENCH, M.D.

Clearwater, Florida

PULMONARY embolism is of frequent occurrence,[1-3] particularly in patients with congestive heart failure.[4-6] The clinical features of thromboembolic phenomena have been well defined in non-cardiac disease,[7,8] but the manner in which pulmonary embolism may disturb congestive heart failure has not been clear. Attention was called to this problem by the development, in a number of patients with pulmonary emboli, of the triad of intractable edema, disproportionate tachycardia and digitalis toxicity. This investigation was undertaken to evaluate the occurrence of this triad in patients who died of chronic congestive heart failure complicated by pulmonary embolism and to compare them with another group of patients with fatal heart failure whose course was not thus complicated.

METHODS

From January 1946 to July 1954, at the Peter Bent Brigham Hospital, forty-seven patients who had congestive heart failure died as a major consequence of multiple pulmonary emboli. The clinical records and autopsy protocols were reviewed, and special emphasis was placed upon a search for evidence of intractable edema, disproportionate tachycardia and digitalis toxicity prior to death. Three additional patients with whom the author had personal experience at the New England Center Hospital were included. The records of fifty patients from the Peter Bent Brigham Hospital who died in congestive failure not complicated by pulmonary embolism were reviewed from the same standpoint. In this group it was necessary to include five postoperative cardiac surgical patients. No patient was included who had experienced a recent myocardial infarction.

That the groups were comparable so far as types of heart disease may be seen from Table I; the etiology of the heart disease in each group was about the same, namely, half rheumatic and half coronary artery disease. Two cases of non-specific interstitial myocarditis were included in the group with pulmonary embolism. Digitalis toxicity was noted by electrocardiography by well established criteria[9] in forty patients and clinically in six more. Tachycardia was diagnosed when the apical rate was more than 110 per minute.

TABLE I

Condition	Pulmonary Embolism Group	Control Group
Coronary artery disease	28	25
Rheumatic heart disease	20	25
Interstitial non-specific myocarditis	2	..

RESULTS

Intractable Edema. Thirty-five patients in the pulmonary embolism group received mercurials as contrasted with thirty-eight in the control group. Thirty-two of the thirty-five in the pulmonary embolism group were refractory to mercurial diuretics as opposed to only ten who were refractory in the control group. (Table II.)

Therefore it seemed that refractoriness to mercurial diuretics suggested the presence of

pulmonary emboli, and a satisfactory diuresis with mercurials appeared to indicate that multiple pulmonary embolization was not present.

Digitalis Toxicity and Tachycardia. The combination of digitalis toxicity and tachycardia was present in twenty-six cases of the pulmonary embolism group and in seven cases of the control group. Thus the coincidence of tachycardia plus digitalis toxicity was well correlated with pulmonary embolization. (Table III.)

Even more convincing was the association of tachycardia, digitalis toxicity and mercurial fastness. This triad was almost invariably associated with pulmonary embolism. (Table IV.)

The electrocardiogram presented distinctive evidence of acute cor pulmonale in only six patients in the pulmonary embolism group; no such evidence was noted in the patients in the control group. In four cases in each group a left-ward shift of the transition zone was noted. It would appear that this change is not reliable evidence of acute cor pulmonale in the presence of congestive heart failure.

Five patients in the embolism group and one in the control group had frank thrombophlebitis.

TABLE II

Condition	Pulmonary Embolism Group			Control Group		
	Refractory to Mercurials	Not Refractory to Mercurials	Mercurials Not Given	Refractory to Mercurials	Not Refractory to Mercurials	Mercurials Not Given
Coronary artery disease	14	1	13	4	13	8
Rheumatic heart disease	17	2	1	6	15	4
Interstitial myocarditis	1	..	1	..	..	..
	32	3	15	10	28	12

TABLE III

Condition	Digitalis Intoxication plus Tachycardia	
	Pulmonary Embolism Group	Control Group
Coronary artery disease	10	2
Rheumatic heart disease	15	5
Myocarditis	1	..
	26	7

TABLE IV

Condition	Mercurial Fastness plus Tachycardia plus Digitalis Intoxication			
	Pulmonary Embolism Group	Mercurials Given	Control Group	Mercurials Given
Coronary artery disease	10	15	0	17
Rheumatic heart disease	9	19	2	21
Myocarditis	1	1	..	..
	20	35	2	38

COMMENTS

The inception of pulmonary embolism, particularly in established congestive heart failure, is not always easy to appreciate. Few patients have the characteristic association of pain, dyspnea and hemoptysis. The following symptoms have been described as signalling the onset of this complication; these symptoms include bouts of palpitation and arrhythmias, syncopal attacks, recurrent and particularly nocturnal episodes of dyspnea, symptoms of acute anxiety, unexplained epigastric distress and anginal syndromes.[5,7,8,10,11] The association of these symptoms with chronic congestive failure has heretofore not been emphasized.

This study calls attention to the possibility of another clue to this development, namely the triad of tachycardia, digitalis intoxication

and resistance to mercurial diuresis. Satisfactory diuresis with mercurials appears to indicate that multiple pulmonary embolization is not present.

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Subcutaneous Emphysema of Gastrointestinal Origin*

HENRY K. OETTING, M.D., N. E. KRAMER, M.D. *and* W. E. BRANCH, M.D.
Los Angeles, California

SUBCUTANEOUS emphysema is a common finding and may develop from four sources: (1) a break in the continuity of the respiratory tract:[1] (2) gas-forming infections;[2–4] (3) atmospheric or intra-abdominal air through a break in the skin, genitourinary tract or peritoneum;[5–9] (4) a rent in the gastrointestinal tract. The importance of considering the latter point of origin when making the differential diagnosis of the cause of subcutaneous emphysema merits emphasis because of the differences in treatment and prognosis.

Two cases are presented of extensive subcutaneous emphysema arising from the intra-abdominal portion of the gastrointestinal tract. A review of the literature on this subject has been made and the reported cases tabulated. A discussion of the etiology, findings, mechanism of development and means of diagnosis is presented.

HISTORICAL OBSERVATIONS

Abeille[10] in 1853 was the first to describe a case of subcutaneous emphysema arising from the gastrointestinal tract. Von Reich[11] reported a most unusual intestinal injury that was accompanied by subcutaneous emphysema in 1859. Demarquay[12] was the first to record this entity following rectal surgery in 1860. In the same year Ericksen and Tatum[13] described perineal emphysema from transrectal cystotomy. Roger[14] gave the first comprehensive review of the general subject of subcutaneous emphysema in 1862 and reported a case arising from tuberculous enteritis with perforation. He cites Bouley and Reynal who observed subcutaneous emphysema in animals from perforation of the intestinal tract due to ingested foreign bodies. Newman[15] had a patient with a ruptured stomach and subcutaneous emphysema in 1868. Lediard[16] in 1877 reported a case similar to that of Roger, of a patient who died from typhoid fever. Poensgen, Kussmaul and Von Recklinghausen[17] described a patient with perforated gastric ulcer and massive subcutaneous emphysema in 1879.

Faber,[18] Nelson,[19] Rankin and Judd,[20] and Finnegan[21] added cases to the literature between 1885 and 1922. Vigyazo[22,23] in 1926 did likewise and mentioned a number of French physicians (LaPointe, Okinczye, Dujavier, Dantin and Bonneau †) who had observed subcutaneous emphysema following appendectomies. Subsequently, a number of cases were reported.

The subject aroused a good deal of interest in the German literature in the 1920's, when the significance of subcutaneous emphysema as an almost pathognomonic sign of perforated peptic ulcer was emphasized.

At the present time a review of the literature resulted in the collection of thirty-four cases which fall into this classification, to which we wish to add two. The original reports of Kappis[24] and Kausche[25] could not be located but they are briefly cited by Vigyazo.[22,23]

CASE REPORTS

In January, 1954, massive subcutaneous emphysema developed after gastrointestinal surgery in two patients under our care. This complication caused us considerable alarm. Neither we nor any of our colleagues had ever witnessed such an event. These cases generated an interest in the subject when the unusualness of the condition was appreciated.

CASE 1. A seventy-seven year old white housewife was admitted to the hospital with a history of bilateral, cramping, hypogastric

† Not listed in Index Medicus or Surgeon General's Report.

* From the Departments of Medicine and Surgery of the Hollywood Presbyterian Hospital, Olmsted Memorial, Los Angeles, California.

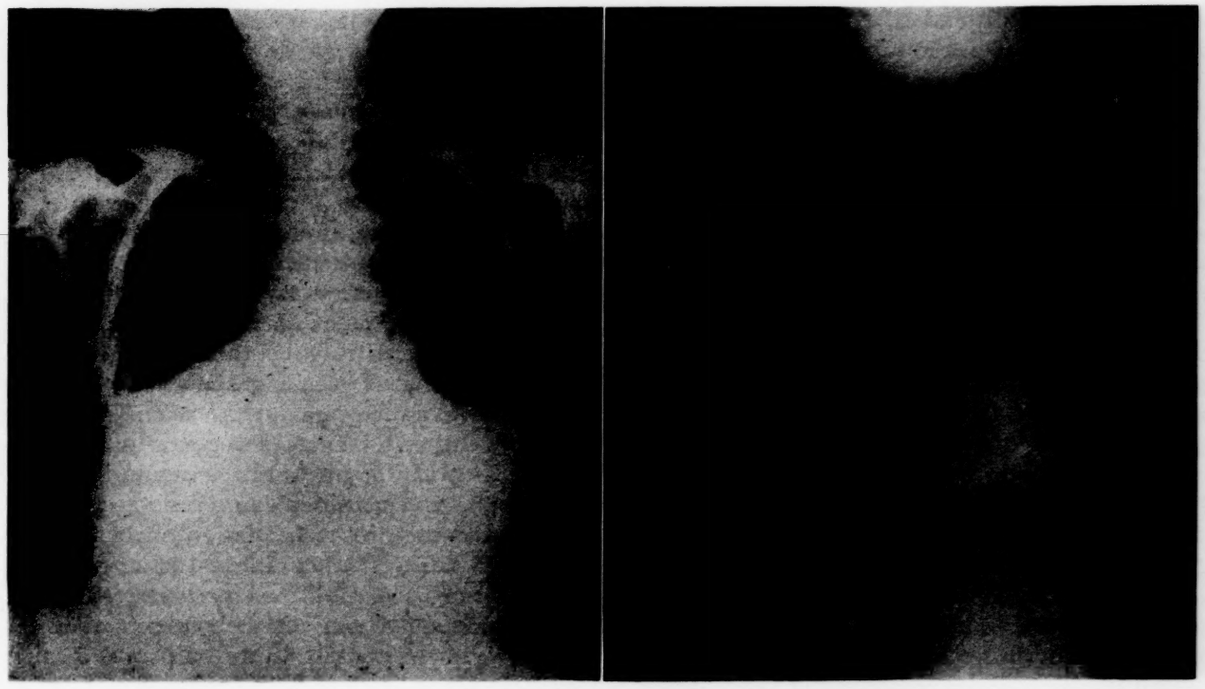

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FIG. 1. Case 1. Radiograph of the chest taken the day of appearance of the subcutaneous emphysema. The widened mediastinum and partial atelectasis of the lower lobes is due to the elevation of the diaphragm from abdominal distention. Mediastinal emphysema is not present. The subcutaneous emphysema extends from the abdominal to the neck areas.

FIG. 2. Case 1. Left lateral radiograph showing the subcutaneous air over the anterior chest, the maximum amount being present over the upper abdomen.

abdominal pain, nausea, vomiting and progressive abdominal distention of five days' duration. Oophorectomy with uterine suspension and elective appendectomy had been performed fifty years before.

Physical examination revealed moderate dehydration and a distended, non-rigid, tender abdomen with absent peristalsis. Blood and urine examinations were normal. Radiographic examination of the abdomen showed classic findings of small intestinal obstruction. After Levin tube suction and intravenous fluid therapy, the abdomen was opened. Endotracheal anesthesia was used.

There were multiple fibrous adhesions from the previous surgery. The ileum was markedly distended. In its distal third several loops were plicated by adhesions that obliterated the lumen. A 2 cm. oval antemesenteric area of intramural gangrene was present at the site of obstruction. The obstructed segment was resected en bloc and a side-to-side anastomosis performed. A 1 per cent solution of neomycin was placed in the lumen of the bowel and the peritoneal cavity. The abdomen was closed in layers and three wire retention sutures placed. Drains were not inserted.

The pathologic diagnosis was acute inflammatory obstruction of the small bowel with insular gangrene of the wall.

Postoperatively the patient passed flatus and stool on the fourth day and was given full oral intake on the fifth day. She remained afebrile until a temperature of 101°F. was noted on the seventh postoperative day. Pyuria and hematuria were discovered on urinalysis at this time and antibiotic therapy was instituted.

Sometime between the evening of the eighth and the morning of the ninth postoperative day, a slightly tender, diffuse, subcutaneous crepitation developed. This extended over the entire anterior abdominal and thoracic wall from pubis to the neck and laterally over the back to the infrascapular region. There were no evidences of disruption of the pulmonary tree clinically. Roentgenographically there was neither mediastinal emphysema, pneumothorax nor pneumoperitoneum. (Figs. 1 and 2.) The ascending colon

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HISTORICAL OBSERVATIONS

Abeille[10] in 1853 was the first to describe a case of subcutaneous emphysema arising from the gastrointestinal tract. Von Reich[11] reported a most unusual intestinal injury that was accompanied by subcutaneous emphysema in 1859. Demarquay[12] was the first to record this entity following rectal surgery in 1860. In the same year Ericksen and Tatum[13] described perineal emphysema from transrectal cystotomy. Roger[14] gave the first comprehensive review of the general subject of subcutaneous emphysema in 1862 and reported a case arising from tuberculous enteritis with perforation. He cites Bouley and Reynal who observed subcutaneous emphysema in animals from perforation of the intestinal tract due to ingested foreign bodies. Newman[15] had a patient with a ruptured stomach and subcutaneous emphysema in 1868. Lediard[16] in 1877 reported a case similar to that of Roger, of a patient who died from typhoid fever. Poensgen, Kussmaul and Von Recklinghausen[17] described a patient with perforated gastric ulcer and massive subcutaneous emphysema in 1879.

Faber,[18] Nelson,[19] Rankin and Judd,[20] and Finnegan[21] added cases to the literature between 1885 and 1922. Vigyazo[22,23] in 1926 did likewise and mentioned a number of French physicians (LaPointe, Okinczye, Dujavier, Dantin and Bonneau†) who had observed subcutaneous emphysema following appendectomies. Subsequently, a number of cases were reported.

The subject aroused a good deal of interest in the German literature in the 1920's, when the significance of subcutaneous emphysema as an almost pathognomonic sign of perforated peptic ulcer was emphasized.

At the present time a review of the literature resulted in the collection of thirty-four cases which fall into this classification, to which we wish to add two. The original reports of Kappis[24] and Kausche[25] could not be located but they are briefly cited by Vigyazo.[22,23]

CASE REPORTS

In January, 1954, massive subcutaneous emphysema developed after gastrointestinal surgery in two patients under our care. This complication caused us considerable alarm. Neither we nor any of our colleagues had ever witnessed such an event. These cases generated an interest in the subject when the unusualness of the condition was appreciated.

CASE 1. A seventy-seven year old white housewife was admitted to the hospital with a history of bilateral, cramping, hypogastric

† Not listed in Index Medicus or Surgeon General's Report.

* From the Departments of Medicine and Surgery of the Hollywood Presbyterian Hospital, Olmsted Memorial, Los Angeles, California.

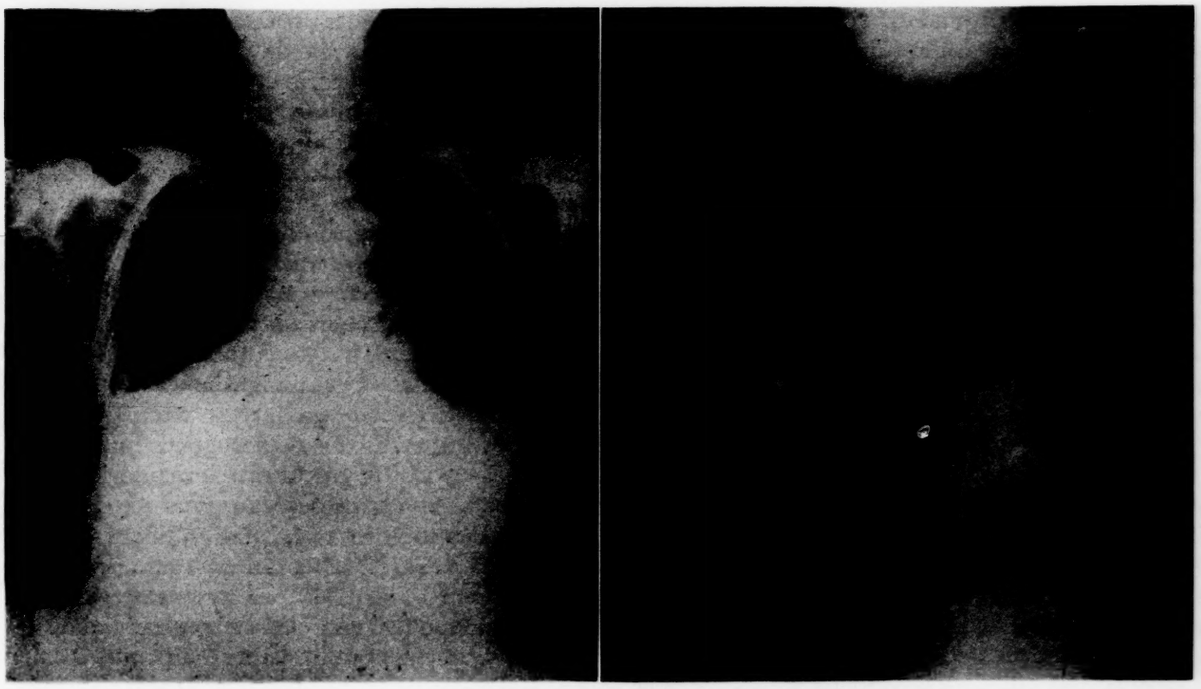

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FIG. 1. Case 1. Radiograph of the chest taken the day of appearance of the subcutaneous emphysema. The widened mediastinum and partial atelectasis of the lower lobes is due to the elevation of the diaphragm from abdominal distention. Mediastinal emphysema is not present. The subcutaneous emphysema extends from the abdominal to the neck areas.

FIG. 2. Case 1. Left lateral radiograph showing the subcutaneous air over the anterior chest, the maximum amount being present over the upper abdomen.

abdominal pain, nausea, vomiting and progressive abdominal distention of five days' duration. Oophorectomy with uterine suspension and elective appendectomy had been performed fifty years before.

Physical examination revealed moderate dehydration and a distended, non-rigid, tender abdomen with absent peristalsis. Blood and urine examinations were normal. Radiographic examination of the abdomen showed classic findings of small intestinal obstruction. After Levin tube suction and intravenous fluid therapy, the abdomen was opened. Endotracheal anesthesia was used.

There were multiple fibrous adhesions from the previous surgery. The ileum was markedly distended. In its distal third several loops were plicated by adhesions that obliterated the lumen. A 2 cm. oval antemesenteric area of intramural gangrene was present at the site of obstruction. The obstructed segment was resected en bloc and a side-to-side anastomosis performed. A 1 per cent solution of neomycin was placed in the lumen of the bowel and the peritoneal cavity. The abdomen was closed in layers and three wire retention sutures placed. Drains were not inserted.

The pathologic diagnosis was acute inflammatory obstruction of the small bowel with insular gangrene of the wall.

Postoperatively the patient passed flatus and stool on the fourth day and was given full oral intake on the fifth day. She remained afebrile until a temperature of 101°F. was noted on the seventh postoperative day. Pyuria and hematuria were discovered on urinalysis at this time and antibiotic therapy was instituted.

Sometime between the evening of the eighth and the morning of the ninth postoperative day, a slightly tender, diffuse, subcutaneous crepitation developed. This extended over the entire anterior abdominal and thoracic wall from pubis to the neck and laterally over the back to the infrascapular region. There were no evidences of disruption of the pulmonary tree clinically. Roentgenographically there was neither mediastinal emphysema, pneumothorax nor pneumoperitoneum. (Figs. 1 and 2.) The ascending colon

was moderately distended. A dome-like pocket of gas was present in the superior portion of the incision. When this pocket was opened, gas with the odor of hydrogen sulfide and approximately 90 cc. of red-brown seropurulent fluid were released. Digital exploration of the wound revealed that the anterior fascial repair was intact. However, in the fascia to the left and lateral to the rectus sheath and superior to the line of suture, a 2 cm. oval defect was felt. The diagnosis of fistula of the small bowel was apparent. Aerobic cultures of the purulent fluid revealed predominantly Aerobacter aerogenes; anaerobic cultures did not yield clostridium organisms.

For the succeeding five days the patient had a low remittent fever which reached 100.6°F. There was no evidence of generalized peritonitis. Antibiotics, parenteral fluid and electrolyte therapy were continued. The subcutaneous emphysema gradually decreased. It disappeared in the areas of the neck and chest by the fifteenth postoperative day. Formed stool was passed per rectum on the seventeenth postoperative day. By the twentieth postoperative day the last remaining traces of the emphysema had disappeared both clinically and radiographically.

Phlebothrombosis of the lower extremities developed and one episode of pulmonary embolism occurred on the twenty-second postoperative day. Anticoagulant therapy was instituted with an uneventful course thereafter. The patient was discharged ambulatory on the forty-eighth postoperative day with complete closure of the fistula.

Comment. Fever on the seventh postoperative day undoubtedly was attributable to the development of the fistula and pyuria. The urine was normal, however, when the emphysema appeared two days later. The subcutaneous emphysema developed rapidly over a twelve-hour period and spread widely from its maximum point in the anterior abdominal wall to the entire trunk and supraclavicular areas. The patient's condition was largely unaltered by the emphysema. Exploration of the intact wound provided an immediate path of escape for the gas and the emphysema no longer progressed. Fever continued until the fourteenth postoperative day and was due principally to the infection at the site of the fistula, but may have been contributed to by the subcutaneous emphysema. During this time the emphysema gradually absorbed, in spite of the continuing infection at the fistula site, and resolved completely by the twentieth postoperative day.

The delay in appearance of the subcutaneous emphysema until the ninth postoperative day eliminated the possibility of a respiratory accident during the endotracheal anesthesia. The absence of physical and radiographic signs of pneumothorax, fractured ribs, blebs and mediastinal emphysema further exonerated the pulmonary tree. There was no roentgenographic evidence of retroperitoneal gas or pneumoperitoneum, and no subcutaneous tissue reaction or evidence of gas gangrene was noted. The dome-like pocket of gas at the wound site was ascribed either to the A. aerogenes infection in the area or to the gas from the fistula, or both. Although A. aerogenes can produce gas, the extent and rapidity of formation of the emphysema, the lack of subcutaneous tissue reaction, the absence of signs of toxicity or enteritis, and the subsequent course of the patient made infection with this organism as the primary cause of the emphysema highly improbable.

We believe that the mechanism of production of the subcutaneous emphysema in this patient was primarily mechanical, i.e., a small bowel fistula broke through the parietal peritoneum, musculature and fascia, and finally connected with the subcutaneous space. Then the peristaltic action of the bowel, together with changes in intra-abdominal pressure, forced diffusion of the gas subcutaneously. Secondarily, the A. aerogenes infection in the fistulous tract and wound site may have contributed to the emphysema. A flap-like valve mechanism cannot be entirely excluded as a factor. However, we believe this highly unlikely in the gradually forming fistula as such flaps occur more commonly with sudden, spontaneous or traumatic perforations of the intestine.

CASE II. A sixty-six year old white housewife was admitted to the hospital with complaints that during the past year she had noted a progressive decrease in the caliber of stools, occasional diarrhea and left lower quadrant abdominal pain almost daily. Diverticulosis of the colon was known to be present for ten years. Sigmoidoscopic examinations were essentially negative. There was no melena. Radiographic studies of the colon, in comparison with those done one year previously, showed that a constricted area of the proximal sigmoid colon had become more irregular, with a narrower lumen. Carcinoma of the colon was suspected. The

patient was prepared for laparotomy and probable colon resection.

Laparotomy was performed under spinal anesthesia through a left rectus incision. A very firm mass, consisting of the sigmoid colon, left ovary and distal half of the left fallopian tube, was found to be adherent to the base of the broad ligament. Several firm nodes were palpable in the mesocolon. The mass was resected widely en bloc, including the mesocolon and peritoneum at the base of the broad ligament. End-to-end anastomosis was performed. The abdomen was closed in layers and four wire retention sutures were placed. Drains were not used.

Pathologic study revealed chronic inflammation with no evidence of malignancy.

Postoperatively the patient became uncooperative and difficult to manage. She passed flatus and stools on the third day. A selected soft diet was started on the fourth postoperative day. During this time, however, tenderness in the left lower abdominal quadrant and a remittent fever up to 100°F. was noted. A left gutter cellulitis was suspected and antibiotic therapy instituted. Rectal examination on the thirteenth postoperative day revealed a bulging, tender mass in the left lateral supralevator quadrant.

Under spinal anesthesia the rectal wall was incised. A soft hissing noise was heard of gas passing through the incision. Digital examination through the wound revealed an ill defined space retroperitoneally and above the levator ani, and a fluctuant area in the cul-de-sac. The incision was extended into the cul-de-sac and 30 cc. of purulent fluid was immediately released. A soft rubber drainage tube was placed in the abscess cavity and sutured to the rectal wall. Cultures were not taken because of gross fecal contamination.

On the evening of the day of operation the patient was restless and pulled out the rectal tube, in spite of the sutures. The temperature was 102°F. There was slight rectal bleeding throughout the first postoperative day. She complained of desire to defecate but attempts to pass even flatus were unsuccessful because of the pain and sphincter spasm. Slightly tender, diffuse subcutaneous crepitation was noted later in the day.

The subcutaneous emphysema extended from the lower abdominal wall to the supraclavicular areas and into the dorsal and lumbar areas of the back. Radiographs of the chest showed traces of air in the anterior mediastinum and the peritoneal cavity. (Fig. 3.) Additional roentgenograms the next day demonstrated an increase in the extent of the subcutaneous emphysema, a localized accumulation of gas in the left pararectal sulcus and retroperitoneal gas surrounding the kidneys and psoas musculature. (Fig. 4.) Antibiotic therapy was intensified. A hard rubber drainage tube was placed high into the rectum.

The patient's temperature gradually decreased to 99°F. in the next five days and remained normal thereafter. There were no complaints referable to the air beneath the skin. The subcutaneous emphysema progressively absorbed so that by the twelfth postoperative day only traces remained and by the fifteenth postoperative day it was completely gone.

On the nineteenth postoperative day, radiopaque medium affirmed and defined the ischiorectal supralevator cavity previously visualized. The next day a radial incision was made through the left side of the anus into the inferior portion of the cavity. Purulent, foul-smelling fluid was released. Laparotomy was then performed. Exploration of the abdominal cavity revealed that the original anastomosis was intact and the mass in the cul-de-sac had disappeared. The left gutter area was well healed with no residual retroperitoneal gas. Pneumatosis intestinalis was not present. A defunctionalizing double-barrelled colostomy was constructed. The patient's course thereafter was uneventful and she became ambulatory and was discharged on the eleventh postoperative day.

Comment. The fever which was present for thirteen days prior to the first rectal surgery was due to the localizing cellulitis in the left gutter area. Following the first rectal operation the patient forceably removed the drainage tube in spite of the sutures. This further aggravated the rectal sphincter spasm and made passage of stool and flatus impossible. While the tube was out, subcutaneous emphysema developed and reached its maximum by the end of the second postoperative day. At this time a noncollapsible tube was placed high in the rectum. This provided an easy exit for the gas in the bowel. Thereafter the emphysema no longer progressed.

The temperature was increased less than one degree by these developments and decreased to normal within five days. The emphysema, of which the patient was hardly aware, gradually

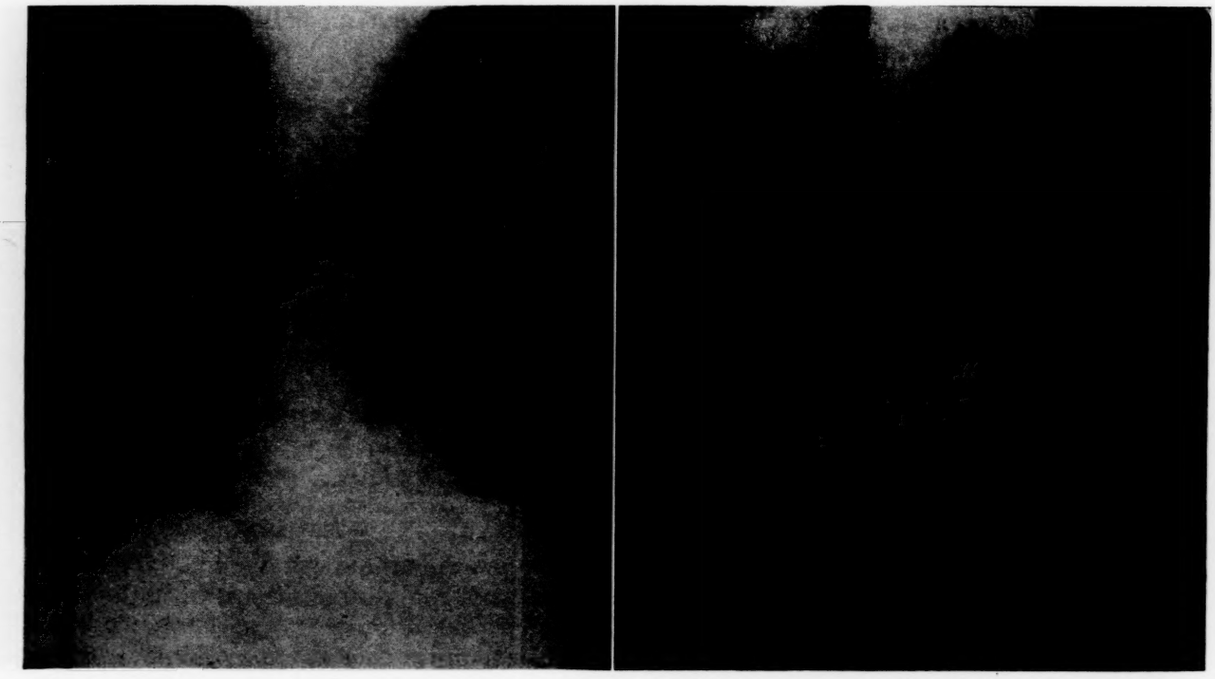

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FIG. 3. Case II. Radiograph of the chest taken the day of appearance of the emphysema showing the subcutaneous gas extending from the neck to the abdominal area, principally on the right side. There are no signs of pulmonary disruption. A faint trace of air is present in the mediastinum.

FIG. 4. Case II. Flat plate of abdomen showing the retroperitoneal and perirenal gas. The gas pocket in the left pararectal sulcus is demonstrated.

absorbed so that by the fifteenth postoperative day it was no longer detectable. The pocket of gas in the left pararectal sulcus became secondarily infected from the cul-de-sac abscess and subsequently had to be drained.

The traces of gas in the anterior mediastinum were not corroborated by other physical or radiographic signs of pulmonary disruption. The presence of gas perirenally and retroperitoneally suggested that the source of the air was inferior to these areas.

The escape of gas on entering the retroperitoneal space at the time of the first rectal operation is not easily explained but may have been due to atmospheric air entrapped in the dead space produced when the left gutter was reperitonized during the initial abdominal operation. On entering the cul-de-sac purulent fluid was obtained but no escape of gas, nor were any gas bubbles mixed with the exudate. The absence of gas upon entering this abscess would seem to indicate very little if any gas formation at this site and certainly not sufficient to produce the subcutaneous emphysema. Furthermore the development of the emphysema very shortly following rectal surgery and not during the localizing phase of the infection seems more than coincidental.

We believe that the mechanism of development of the subcutaneous emphysema in this case was primarily mechanical, i.e., the operation produced a passageway from the lumen of the bowel to the retroperitoneal space. Then in the presence of a marked sphincter spasm great increases in the intraabdominal pressure from ineffectual attempts to pass flatus together with the peristaltic action of the bowel caused sufficient pressure to force the gas into the retroperitoneal area. The air then diffused both transversely to the anterior abdominal wall and superiorly through the mediastinum to the supraclavicular and neck areas. Here, too, a flap-like valve action of the rectal incision could have occurred but this would not materially alter our hypothesis.

ANALYSIS OF TABULATED CASES

Between 1853 and 1953, thirty-four cases of subcutaneous emphysema of gastrointestinal origin have been reported. Age of occurrence

TABLE I

SUMMARIZATION OF REPORTED CASES

Author	Age, Sex	Diagnosis	Operation	Course	Bacteriology	Modus Operandi
Abeille, 1853[10]	24, M	Multiple perforations of colon, etiology undetermined	None (autopsy)	Tumefaction in R.L.Q. with appearance of S.Q.* emphysema on 14th day of illness; incision with release of fetid gas and purulent exudate; emphysema spread to entire body by 15th day; died	None	None offered; 2 points of perforation in cecum with localized peritonitis and fistula formation; generalized peritonitis
Von Reich, 1859[11]	28, M	Traumatic perforation of intestine with disruption of abdominal wall musculature; skin intact	None (autopsy)	Day after injury emphysema appeared on anterior abdominal wall and spread to nipple and inguinal lines; died on 4th day after injury	None	None offered; 3 inch rent through fascia and muscle of abdominal wall; peritonitis with perforated ileum adherent to muscle wound
Demarquay, 1860[12]	?, M	Anal fistula	Incision of fistula	Emphysema developed in perineum, scrotum and lower abdomen 48 hours postoperatively; gradually absorbed; recovered	None	Intrarectal dressing caused sphincter spasm; patient's efforts to pass flatus forced gas into S.Q. spaces
Tatum, 1860[13]	72, M	Urinary retention due to urethral stricture	Cystostomy via rectum (autopsy)	Emphysema of scrotum on 1st day postoperatively with extension as high as axilla by 2nd postoperative day; died	None	None offered
Ericksen, 1860[13]	32, M	Urinary retention due to urethral stricture	Cystostomy via rectum (autopsy)	Stormy with tachycardia, chills and delirium; emphysema appeared on 5th postoperative day over posterior thighs, flanks, right shoulder and arm to wrist	None	Valvular action of rectal flap; fecal odor to gas; retroperitoneal air in pelvis
Roger, 1862[14]	12, M	Tuberculous enteritis with perforations of cecum and ileum with localized and generalized peritonitis	None (autopsy)	Tumefaction in left side of abdomen with S.Q. emphysema on 11th day of illness; spread across abdomen and superiorly to involve the entire right side of body, neck and face; on 12th day pneumonia and death	None	Adherence of ileum to anterior abdomen wall with perforation through adhesion and peritoneum and passage of gas to S.Q. spaces
Newman, 1868[15]	30, M	Ruptured stomach, pneumoperitoneum	None (autopsy)	Violent vomiting; pneumoperitoneum and S.Q. emphysema in neck and right arm 14 hours after onset; emphysema increased before death to include all of body except left arm and legs; died	None	Linear abrasions of peritoneum found at autopsy; pressure of pneumoperitoneum sufficient to cause diffusion of gas through these abrasions and then to subcutaneous areas
Lediard, 1877[16]	21, F	Typhoid fever with perforation of ileum and localized peritonitis	None (autopsy)	Stormy course; diffuse emphysema starting 9th day and advancing to 19th day—the day of death	None	Walled off accumulation of feces with erosion of the anterior abdominal wall; perforated ileum in mass; gas diffused into S.Q. spaces
Poensgen, Kussmaul and Von Recklinghausen, 1879[17]	?	Perforated ulcer of cardia of stomach	?	?	?	Spread of gas through the esophogeal hiatus into the mediastinum, the neck and adjacent subcutaneous spaces
Faber, 1885[18]	?	Perforated gastric ulcer	?	?	?	Perforation into mediastinum with spread of gas into neck, etc.
Faisst, 1920[28]	?	Anterior abdominal wall laceration	?	Emphysema of scrotum	?	Perforation of ulcer in loop of small intestine in area of abdominal wall injury

*S.Q. = subcutaneous.

TABLE I (*Continued*)

Author	Age, Sex	Diagnosis	Operation	Course	Bacteriology	Modus Operandi
Nelson, 1920[19]	54, M	Intestinal obstruction pneumoperitoneum	Laparotomy	No perforation discovered; tube drainage of pneumoperitoneum; recovered	None	None offered
Rankin and Judd, 1922[20]	46, M	Vesicocolic fistula due to perforated diverticulum of colon with obstruction of colon	Colostomy	8th postoperative day gas in scrotum; colostomy then opened; no emphysema on abdominal wall; benign course; survived	None	Secondary perforation of colon into abdominal wall with passage of gas down into scrotum
Finnegan, 1923[21]	42, M	Traumatic (pneumatic) rupture of rectum	None	No pneumoperitoneum; survived	None	Rapid spread of air up retroperitoneal spaces to neck and supraclavicular spaces
*Kausche, 1923[25]	?	Perforation of posterior wall duodenal ulcer	?	Phlegmonous inflammation with subcutaneous emphysema	None	None
*Kappis, 1924[24]	?	Postoperative perforation of bowel	?	Anterior wall emphysema	None	Pneumoperitoneum with passage of gas through traumatic holes or breaks in parietal pneumoperitoneum and then into subcutaneous spaces
Vigyazo, 1926[22]	52, M	Perforated anterior wall duodenal ulcer lesser curvature	Perforation closed	Emphysema present on admission in umbilical area; slight fever and tachycardia; resolution of emphysema in 1 day; recovered	None	(1) Gas into the subserosal area to the retroperitoneal area then to the anterior abdominal wall; (2) gas passing into leaves of hepatoduodenal ligament into the periportal tissue and then via the round ligament to the periumbilical area; (2) a projectile-like passage of gas via the route in (1)
Vigyazo, 1926[22]	?	?	Gastroenterostomy	Benign emphysema gone in a few days; recovered	?	?
Vigyazo, 1926[22]	?	Appendicitis	Appendectomy	Benign S.Q. emphysema disappeared in a few days; recovered	?	?
Podlaha, 1926[27]	73, M	Perforated gastric ulcer in cardia	Perforation closed	Benign; emphysema resolved in 5 days; recovered	None	Emphysema first appeared in supraclavicular areas; spread via esophageal hiatus and mediastinum
Korach, 1927[28]	36, M	Perforated gastric ulcer on lesser curvature	None (autopsy)	Emphysema present on admission; died	None	Emphysema periumbilical first and rapidly advanced, even after death; gas burned with blue flame and said to be hydrogen
Speed, 1931[29]	50, M	Fracture of right rami of ischium; rupture of ampulla of rectum; fracture of sacrum	Incision and drainage of ischiorectal abscess	Rapid development of scrotal and subcutaneous emphysema; emphysema gone on 25th day; recovered	None	Minute traumatic perforation of rectal ampulla with passage of gas into the scrotum and then into S.Q. spaces in area of right iliac crest and thigh
Barrington and Gardham, 1932[30]	52, M	Intestinal obstruction and emphysematous gangrene of left leg	None (autopsy)	Emphysema of left thigh from Poupart's ligament to knee and scrotum on admission; died 3 hours afterward and on 5th day of illness	Bacillus coli	Perforation of descending colon into retroperitoneal area; gaseous necrosis of muscles of thigh, iliacus and psoas
Gruca, 1933[31]	?	Acute phlegmonous appendicitis	Appendectomy	R.L.Q. emphysema present on admission	?	?

* Original reference not available to us. Cited by Vigyazo.[22,23]

TABLE I (*Continued*)

Author	Age, Sex	Diagnosis	Operation	Course	Bacteriology	Modus Operandi
Baumecker, 1941[33]	67, M	Carcinoma of left colon	Resection with side-to-side anastomosis	Benign course; 2nd postoperative day emphysema in S.Q. tissues; fistula then formed and spontaneously healed; emphysema absorbed in 3 weeks; recovered	None	Perforation of bowel; gas to wound site via fistula and then to S.Q. spaces
Hasselbach, 1941[34]	67, M	Inoperable carcinoma of sigmoid colon	Exteriorization of colon with cautery, perforation of proximal loop	S.Q. emphysema in 6 hours after cauterization; afebrile; emphysema gone by 17th postoperative day; survived	None	(1) Suture perforation with leak into S.Q. space; (2) deep accidental cautery perforation with S.Q. leak; (3) too firm a dressing over exteriorized loop causing gas to go into S.Q. spaces
Brown and Hinton, 1946[35]	47, M	Papillary cystadenocarcinoma of sigmoid colon	Resection of colon; reperitonealization of left lumbar gutter not possible	Febrile with peritonitis; S.Q. emphysema on 11th postoperative day; pneumoperitoneum on 21st postoperative day; emphysema gone on 24th postoperative day; recovered	B. coli communior; non-hemolytic streptococcus	Infection due to leakage of anastomosis with gas production and finally fistula formation
Dawson and Hardy, 1948[36]	73, F	Diverticulitis with emphysema and cellulitis	Excision of neurofibroma; incision of subcutaneous abscess; colostomy (autopsy)	Developed left inguinal abscess with crepitant cellulitis in thigh and perineum; afebrile; frothy, foul pus; fecal fistula developed; partial obstruction of colon—colostomy; general peritonitis	B. coli; Streptococcus fecalis	Perforation of diverticulum into pelvic retroperitoneal area; secondary superficial cellulitis followed by fistula formation
McCorkle and Stevenson, 1937[32]	62, M	Perforated anterior wall duodenal ulcer	Closure of perforation	Pneumoperitoneum and emphysema of mediastinum, neck and chest wall postoperatively; peritonitis; died 8th postoperative day	None	Pneumoperitoneum with spread via the mediastinum to the neck and thorax; no retroperitoneal air or gas in ligamentous tissue noted at surgery
Burt, 1949[37]	38, F	Foreign body giant cell granuloma of rectum, due to injected lipoidal substance	Local resection	Fever, abdominal distention; stool per rectum; S.Q. emphysema on 3rd postoperative day; laparotomy; gas in subperitoneal tissues and mesentery of colon; S.Q. emphysema gone 6th postoperative day; recovered	B. coli	Diffusion of gas from intestinal lumen along rectovaginal or retrorectal tissues to mesenteries; then diffusion through thinned-out portions of fascia to S.Q. position
Hammesfahr, 1949[5]	?	Rectal tear due to trauma	Closure of perforation	Localized pocket of emphysema in gluteal muscle; benign; recovered	Sterile	None
Hachmeister, 1951[38]	59, M	Appendicitis; Meckel's diverticulum	Appendectomy; resection of Meckel's diverticulum	Uneventful emphysema gone in 2 days; recovered	None	Leakage of suture with resulting pneumoperitoneum with diffusion into S.Q. tissues
Heinrichs, 1951[39]	50, F	Inflammatory tumor of pelvis with stenosis of sigmoid colon	Drainage; resection of sigmoid; end-to-end anastomosis and right-sided colostomy	24-hour pain in chest and cyanosis; no chest findings; 48-hours later emphysema in neck and thorax (3rd postoperative day); emphysema absorbed in about 14 days; recovered	No anaerobic growth; B. coli enterococcus	Leak of suture line with passage of gas into retroperitoneal area at site of anastomosis and then up mediastinum into neck
Borgström, 1953[40]	66, F	Fecal polyps and traumatic perforation	Diagnostic biopsy via proctoscope; closure of perforation	Rapid onset of emphysema; fever; abdominal distention; emphysema gradually disappeared; recovered	B. coli	Entrance of air into the retroperitoneal space and subsequent spread via mediastinum to the neck area and over thorax

ranged from twelve years to seventy-three years. Well over one-half of the patients were males. The exact rate of incidence is unknown. (Table I.)

The etiologic diagnoses were diverse but in all instances the intestinal tract was perforated, although Nelson was unable to determine the site of the perforation. The principal diagnoses were perforated peptic ulcer in seven cases (20.6 per cent); traumatic perforation in seven cases (20.6 per cent); appendicitis in three cases (8.8 per cent); carcinoma and intestinal obstruction, each three cases (8.8 per cent); diverticulitis and bacterial enteritis in two cases each (5.8 per cent); one instance of anal fistula (2.9 per cent) and miscellaneous diagnoses six cases (17.6 per cent). (Table II.)

TABLE II
ETIOLOGIC DIAGNOSES

	No. of Cases	Per cent of Total
Perforated peptic ulcer	7	20.6
Trauma	7	20.6
Enteritis	2	5.8
Intestinal obstruction	3	8.8
Diverticulitis	2	5.8
Appendicitis	3	8.8
Carcinoma	3	8.8
Anal fistula	1	2.9
Miscellaneous and unknown	6	17.6

The large intestine was the most frequent site of perforation, with nineteen cases (55.9 per cent) falling into this category. The stomach was involved in six cases (17.6 per cent); the duodenum in three (8.8 per cent); the jejunum or ileum in four (11.6 per cent); the appendix in three (8.8 per cent); the colon in eight (23.2 per cent); the rectum or anus in eight (23.8 per cent), and unknown sites in two cases (5.8 per cent). (Table III.)

The correlation between the site of first appearance of the subcutaneous emphysema or the area of maximum involvement and the site of perforation in the intestinal tract is noteworthy. Emphysema of the anterior abdominal wall was associated with perforation of the small intestine in 4 cases, appendix in 3 and colon in 5. Emphysema of the scrotum, perineum or thigh was usually associated with tears in the anorectal area or colon.[5] Supraclavicular emphysema was most common with perforated gastric ulcers. (Table IV.)

In nineteen cases (55.9 per cent), the subcutaneous emphysema occurred before surgery and provided an additional sign for diagnostic evaluation. Fifteen (44.1 per cent) of the cases developed postoperatively. The most common preoperative causes were perforated peptic ulcers, seven cases (20.6 per cent); traumatic perforation, five cases (14.7 per cent) and appendicitis, three cases (8.8 per cent). After surgery the subcutaneous emphysema occurred most often as a direct result of the operation or following leakage of suture lines, fistulas or peritonitis. (Table V.)

TABLE III
ANATOMIC SITE OF PERFORATION

	No. of Cases	Per cent of Total
Stomach	6	17.6
Duodenum	3	8.8
Jejunum and ileum	4	11.6
Appendix	3	8.8
Colon	8	23.2
Rectum and anus	8	23.2
Unknown	2	5.8

TABLE IV
RELATIONSHIP OF AREA OF FIRST APPEARANCE OF EMPHYSEMA TO SITE OF PERFORATION

Organ	Anterior Abdominal Wall	Perineum, Scrotum or Thigh	Supra-clavicular or Neck Area	Other Areas
Stomach	2	0	4	0
Duodenum	1	0	1	1
Ileum or jejunum	4	1	0	0
Appendix	3	0	0	0
Colon	4	3	1	0
Rectum or anus	0	4	2	2
Unknown	0	0	0	1

Infection preceded the occurrence of subcutaneous emphysema in sixteen cases (26.4 per cent). There was no apparent infection before the development of the emphysema in eighteen patients (53.0 per cent). In all of these latter patients emphysema developed within forty-eight hours after the onset of their illness or operation. Twelve of the sixteen cases with infection required from forty-eight hours to fourteen days for the emphysema to appear. (Table V.)

In none of the cases, with the exception of

Kausche,[25] Dawson[36] and Hardy and possibly Abeille,[10] was mention made of skin or subcutaneous tissue reaction. The cultural results are tabulated. There were no unusual organisms found—only those one might expect in any gastrointestinal tract. No one reported isolation of members of the clostridium group.

TABLE V
RELATIONSHIP OF EMPHYSEMA TO ONSET OF ILLNESS OR SURGERY AND INFECTION

	No. of Cases	Per cent of Total
Emphysema before surgery	19	55.9
Emphysema after surgery	15	44.1
Pre-existent infection before emphysema	16	26.4
No infection before emphysema	18	53.0
Emphysema within 48 hours of surgery or illness	22	64.7
With infection	4	11.6
Without infection	18	53.0
Emphysema after 48 hours of surgery or illness	12	35.3
With infection	12	35.3
Without infection	0	0.0

The extent of subcutaneous emphysema ranged from a localized process a few centimeters in diameter to massive involvement of the trunk, neck and face. The degree of emphysema bore no apparent relation to the diagnosis. In most instances the emphysema was not massive. The period of resolution of the emphysema was roughly dependent on its maximum extent and complete absorption took from twenty-four hours to three weeks. Sequelae attributable to the emphysema were not reported.

The course of the patients was quite variable. The subcutaneous emphysema itself produced no set pattern of clinical response. Many of the patients had a slight elevation of temperature and an increase in pulse rate for a day or two. The course and prognosis was more dependent on the basic nature of the disease or postoperative complication.

Seventeen (50.0 per cent) of the reported cases survived and eleven (32.4 per cent) of the patients died. In six cases the outcome is unknown but probably one of these patients also survived.[31] In only one of the nine cases reported since 1938 did the patient succumb.

The explanations of the mechanisms as offered by the various authors are briefly listed. A more detailed discussion of the mechanism of development of subcutaneous emphysema derived from an analysis of the reported cases, our experience with two patients and more recent physiologic considerations follows.

Cases of subcutaneous emphysema due to postlaparotomy pneumoperitoneum have been reported by Baumecker[7] and others[6,23,24,41] but are not truly of gastrointestinal origin and are, therefore, not included here.

POSTULATED MECHANISM

The pathogenesis of subcutaneous emphysema of gastrointestinal origin is dependent on three basic factors: perforation of the bowel; an adequate pressure gradient between the lumen of the bowel and ultimately the subcutaneous space; and the anatomic site of perforation. Infection, if present, may be an additional factor.

Perforation of the intestinal wall may occur after peptic ulceration, infection, chemical, mechanical, irradiative, pneumatic and surgical trauma and neoplasia. These are selfexplanatory and need no elaboration. Partial perforation with subsequent intestinal pneumatosis is not discussed here.[42]

Accurate pressure recordings in the lumen of the intestine and the adjacent abdominal cavity have revealed that peristaltic movements produce large pressure gradients between these areas. Such gradients are sufficient to perforate weakened portions of the wall and discharge intestinal contents into the abdominal cavity or retroperitoneal space. Expulsion of intestinal content at pressures exceeding atmospheric is possible by the contractions of the intestine alone, as evidenced by the regurgitation of gastric fluids or the involuntary passage of flatus or feces. The intra-abdominal pressure may be greatly increased by the contraction of the diaphragmatic and abdominal muscles. This increased pressure is transmitted to the contents of the intestinal tract and promotes their evacuation, especially at sites of perforation when the sphincters are intact.[43,44]

Resistance of the tissues to diffusion of gas varies with their density. Solid parenchymatous organs and serous membranes have a relatively great resistance to the diffusion of air, whereas loose areolar and fascial structures readily allow the passage of gas. If the latter types of tissue are adjacent to a perforation in the intestinal tract, a relatively great pressure dif-

ferential is established and emphysema may develop. In postoperative cases the pressure gradient may be enhanced by the presence of "dead spaces." In addition movement of the tissues in the wound site and in proximity to an intestinal perforation may increase the pressure differential and promote development of subcutaneous emphysema.[2]

The anatomic site of perforation largely determines the route of escape of the gas to the subcutaneous position. Gastric ulcers, particularly in the cardia, may perforate directly into one of the diaphragmatic hiatuses, tissues contiguous with them, or the retroperitoneal space. This would allow diffusion of the gas via the mediatinum to the supraclavicular and upper anterior chest areas. With partial perforations gas may pass from a subserous position to the aforementioned structures. Podlaha[27] placed hydrogen peroxide beneath the serosa of the cardia of the stomach and observed the gas to pass via the paraesophageal ligaments to the aortic notch and then into the mediastinum and supraclavicular area.

Subcutaneous emphysema due to perforations of anterior wall duodenal ulcers may develop by several routes. Podlaha[27] showed by the injection of hydrogen peroxide into the subserosa in the area of the pylorus that the gas bubbles passed to the hepatoduodenal and round ligaments and then to the periumbilical subcutaneous position. As proposed by Vigyazo,[22,23] a flap-like valve perforation could allow gas in the subserosal area to move posteriorly around to a retroperitoneal position, and from there to subcutaneous spaces of the anterior abdominal wall. A very sudden projectile force, and without a valve action, could produce emphysema by the same route. Posterior duodenal ulcers which have perforated allow the gas to enter the retroperitoneal position and then diffuse transversely to the anterior abdominal wall (the patient is usually lying supine in bed) or via the mediastinum to the areas at the base of the neck.

It has been observed that when the small or large intestine has been perforated the emphysema most often appears first on the anterior abdominal wall and is usually maximum close to the site of perforation. This is certainly true in acute appendicitis, and perforations of the colon ordinarily follow this same pattern. However, as in the cases of Rankin and Judd,[20] and others,[30,36] the emphysema may first become apparent in a distant area, e.g., scrotum or thigh. The usual route of exit of the gas from the bowel is directly through a pathologic defect in the parietal peritoneum or tissues contiguous with this defect into the intermuscular planes and subcutaneous spaces. Rarely, the gas may pass from the subserous position between the leaves of the mesentery to the root of the mesentery retroperitoneally and then to the subcutaneous position.[37,45]

When the perforation occurs in the anorectal area, the gas passes either to the anterolateral retroperitoneal space or to the retrorectal area. From these positions it may pass via the intermuscular planes to the subcutaneous areas of the perineum, scrotum, buttocks or lower abdominal wall; or superiorly through the paravertebral retroperitoneal tissues into the mediastinum and then into the supraclavicular and neck areas. Defects above the line of the pelvic reflection of the peritoneum may in addition produce pneumoperitoneum.

The development of subcutaneous emphysema associated with pneumoperitoneum is difficult to comprehend.[19] In postlaparotomy cases the emphysema has been explained by Baumecker[7] and others[6,8,44,46] as due to diffusion of the air through the suture holes, inadvertent tears in the parietal peritoneum and/or slow healing of the peritoneum. McCorkle and Stevenson[32] proposed in their case that the gas in the abdominal cavity traversed into the mediastinum but they found no gas in the ligamentous structures. With sufficient gas pressure in the abdominal cavity it would be anatomically possible for the gas to escape through the loose areolar tissue in the paraesophageal area into the mediastinum. As has been shown in dogs, a thinned-out parietal peritoneum at the internal inguinal ring or in a hernial sac, if present, could be other possible routes.[47] It has been ascertained that therapeutic as well as postoperative pneumoperitoneum is rarely complicated by subcutaneous emphysema.[48] Its occurrence must depend on some area in the parietal peritoneum being unusually thin or weak and easily, perhaps minutely, ruptured by the pressure of the gas in the abdominal cavity.

Infection plays a part in the development of subcutaneous emphysema in two ways. First, infection may cause perforation of the bowel, as in typhoid fever, and lead to local or generalized peritonitis with fistula formation. It may complicate any intestinal surgical procedure

with similar results. Second, certain bacilli may be gas-forming and contribute in varying degrees to production of the emphysema.

Most of the enteric organisms and also anaerobic staphylococci have the ability to produce gas in the presence of glucose. Exceptions are Salmonella typhosa, the shigella group and Pseudomonas aeruginosa together with staphylococci and streptococci within the intestinal tract, which do not produce gas with the common sugars.[49] The latter, therefore, need not be considered as a direct cause of subcutaneous emphysema.

The saprophytic clostridial organisms are capable of maintaining themselves in the intestinal tract of man. Some authorities indicate that Clostridium perfringens (welchii) is invariably present in normal human feces.[50] The production of fibrinolysins, hyaluronidase, collagenase and the toxic enzyme lecithinase by these bacilli promotes the passage of gas through the fragmenting connective tissue surrounding the muscle bundles and in the subcutaneous space and produces the entity of gas gangrene. Its occurrence has been reported after gastrointestinal and other surgery, but this is rare. It is much more commonly associated with trauma when the almost essential factors of shattered tissue and contamination with soil or other foreign material is present.[49]

Certain clinical observations seem to relegate infections with gas-forming organisms to no more than a contributory role in the production of subcutaneous emphysema. Frequently the amazing speed with which emphysema occurs and the volume of gas necessary for its widespread distribution is much beyond the biologic capabilities of such organisms. Also, the gradual resolution of the emphysema in the presence of continuing infection, its occurrence only after a disruption of the bowel, the benign nature of the emphysema, and its progression despite the susceptibility of many of these organisms to intensive antibiotic therapy would all seem to support the hypothesis that infection is not the principal cause of subcutaneous emphysema. The primary requirement is the presence of an adequate pressure gradient between the lumen of the bowel and tissues adjacent to the perforation capable of transmitting air.

Perforation of the intestinal tract occurs commonly. Why then is the complication of subcutaneous emphysema so rare? Several factors may be the explanation. The site of perforation may not be contiguous to loose areolar tissue or adhesions, or ligaments capable of transmitting the gas. Apparently in most cases the gradient between the intraluminal gas pressure and the tissue resistance to the spread of the gas is insufficient to allow emphysema to develop. The resistance of the sphincters at the normal routes of escape may be less than that of the tissues at the potential site of emphysema formation. Rapid healing of the site of perforation may prevent passage of sufficient gas to produce clinically detectable emphysema. Also, in the case of fistula formation the skin breakdown may be rapid and thereby allow a direct and easy exit for the gas. Certain therapeutic measures, such as rectal and gastric tubes and prompt opening of wound infections, facilitate passage of gas through these routes rather than into the tissues surrounding the perforation. Use of antibiotics postoperatively tends to prevent and eliminate infection which would cause the complications necessary to allow the development of subcutaneous emphysema.

DIAGNOSIS

The diagnosis of the cause and source of subcutaneous emphysema may be established from the history of the patient, nature of the surgery or injury, if any, characteristics of the emphysema, abdominal findings and elimination of the respiratory tree as the site of the disturbance.

In questioning the patient particular reference must be made to those conditions leading to perforation, among which peptic ulcer, appendicitis, diverticulitis, ingestion of foreign bodies and bacterial enteritis are the most common. As a postoperative complication subcutaneous emphysema is most likely to occur after operation or injuries which perforate or interrupt the continuity of the bowel. If infection is present at the time of surgery, disruption of suture lines and fistula formation must be considered as further instigating complications.

The rate of development of emphysema gives one a clue as to the pathogenesis of the perforation. A rapid diffusion of subcutaneous emphysema over a period of minutes to forty-eight hours after operation or the onset of the illness indicates a spontaneous or mechanical perforation of the bowel as the cause. Subcutaneous emphysema developing from forty-eight hours to days after the beginning of the illness or postoperatively is most likely due to an under-

lying infection which has caused perforation with peritonitis or fistula formation.

The first site of appearance or area of maximum development of subcutaneous emphysema suggests the approximate anatomic level of perforation of the bowel. Localized periumbilical emphysema is almost pathognomonic of perforation of an ulcer at or near the pylorus. Supraclavicular and neck emphysema with or without more extensive involvement of the trunk points first to a tear in the rectal area and secondly the perforation of a posterior duodenal ulcer. Gastric ulcer with perforation in approximation to one of the diaphragmatic hiatuses also must be considered in this situation but is rare and comprises only 1 to 2 per cent of all perforated ulcers. Localized or subcutaneous emphysema maximal on the anterior abdominal wall, in the absence of wound infection, indicates the small intestine or colon as the site of the defect. When the emphysema is greatest in the perineum, gluteal area, scrotum, thigh or lower abdominal wall, a tear in the anus or rectum is most likely.

Perforation of the intestinal tract within the peritoneal cavity gives rise to abdominal findings of localized or generalized peritonitis, pneumoperitoneum, tumefaction or fistula formation. These signs are usually absent when the rectum or anus is perforated and may be so with posterior duodenal or gastric ulcers. Roentgenographic examination of the abdomen is invaluable in determining the presence of retroperitoneal gas. The use of the proctoscope will define the exact site of the perforation in the lower bowel.

It has been observed repeatedly in patients and proved in dogs that air beneath the skin is itself a benign condition.[47] McNab[52] reported a child who lived ten years with generalized subcutaneous emphysema. Ordinary subcutaneous emphysema causes practically no tissue reaction. One may expect the patient to show a slight increase in temperature and pulse rate with the development of subcutaneous emphysema. More than this must be explained by other pathologic processes.

The rare possibility of gas gangrene must be considered. Its diagnosis rests primarily on clinical grounds. Black, friable, necrotic tissue with a surrounding zone of erythema, a foul discharge containing bubbles of gas, signs of increasing toxicity, progressive advance of the emphysema and radiographic demonstration of gas bubbles in the muscle bundles are the chief diagnostic characteristics of gas gangrene. The mere presence of Cl. perfringens, Clostridium novyi or other members of the group, as demonstrated on stained smears or culture, does not necessarily lead to and therefore indicate the existence of gas gangrene.[49]

In any event the respiratory trees must be freed of suspicion as the originating site of the emphysema.[53] The patient must be questioned as to causes of sudden increases in intrapulmonic pressure such as vomiting, straining at stool, cough and thoracic injury. The presence or absence of an infection in the respiratory tree must be determined. A search for ulceration of the oropharynx, trachea or esophagus should be made, particularly postoperatively when endotracheal anesthesia has been used. The presence of physical and radiographic evidence of atelectasis, pneumothorax, mediastinal widening or thoracic injury usually indicates that the emphysema is arising from a break in the pulmonary tract.

Subcutaneous emphysema of respiratory origin is most often limited to the face, neck, supraclavicular and upper thoracic areas. Emphysema in other areas makes the gastrointestinal tract a more likely source. In some cases there may be evidence of mediastinal emphysema clinically or radiographically which would tend to confuse the issue. However, in these situations the history, absence of other signs of respiratory disease, presence of abdominal signs compatible with perforated viscus, and proctoscopic examination will give one the correct diagnosis of the site of origin of the subcutaneous emphysema.

TREATMENT AND PROGNOSIS

Subcutaneous emphysema of gastrointestinal origin requires little or no treatment. The patients have practically no subjective complaints referable to the emphysema. If the emphysema should increase progressively and cause constrictive symptoms and findings in the neck or thorax, tension pneumothorax must again be ruled out. If treatment of the emphysema is deemed necessary, mild sedation and prophylactic gas bacillus antitoxin may be used. Multiple incisions or punctures of the skin were abandoned long ago. Therapy must be directed primarily toward the cause of the emphysema within the abdominal cavity as the prognosis of

the patient will depend on the skillful management of the perforated viscus.

SUMMARY AND CONCLUSIONS

1. A review of the literature on subcutaneous emphysema of gastrointestinal origin is presented, together with a tabulation of thirty-four previously reported cases.

2. Two additional cases are described. In one instance the subcutaneous emphysema developed from a small bowel fistula; in the other, rectal surgery had been performed.

3. An analysis of the cases in the literature is made, indicating the relationship of age, sex, diagnosis, areas of emphysema, sites of perforation, course of the patient and bacteriology.

4. The occurrence of subcutaneous emphysema arising from the gastrointestinal tract is most unusual. Its exact rate of incidence is unknown.

5. The physiologic considerations, anatomic routes of escape of the gas to the subcutaneous position and role of infection are discussed.

6. The presence of subcutaneous emphysema as an aid in the diagnosis of perforation of various levels of the gastrointestinal tract and its significance as a pathognomonic sign in perforated peptic ulcers are defined.

7. The benignity of subcutaneous emphysema and dependency of the prognosis on the basic underlying condition are indicated.

8. The treatment of subcutaneous emphysema of gastrointestinal origin is expectant and symptomatic. Therapy must be directed primarily toward the more serious intraabdominal perforation.

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Association of Antibody-coated Red Blood Cells with Ulcerative Colitis*

Report of Four Cases

MORTIMER LORBER, M.D., LAWRENCE I. SCHWARTZ, M.D. *and* LOUIS R. WASSERMAN, M.D.
New York, New York

THE anemia frequently associated with ulcerative colitis is ordinarily attributed to chronic blood loss and diminished erythropoiesis secondary to chronic infection.[1a] There is the further possibility that an additional autoimmune hemolytic component occurs in some patients. We have recently had the opportunity of observing four patients with ulcerative colitis in whom a positive direct Coombs reaction[1b] was in fact, demonstrated. This article is a report of these cases, with a discussion of the possible relationship between the antibody-coated red cells and the intestinal disorder.

CASE REPORTS

CASE 1. Mrs. L. S. (No. 19691), a twenty-eight year old Negro, was admitted to The Mount Sinai Hospital December 11, 1953. The patient had been in good health until one year prior when frequent bloody bowel movements developed. Five months later because of an exacerbation of symptoms, associated with marked anemia, she received four blood transfusions at another hospital. Six weeks before admission a severe relapse occurred and three days prior to admission nausea and vomiting developed.

On physical examination the patient appeared pale and chronically ill. The findings were otherwise within normal limits. No icterus was present.

Blood examination revealed a hemoglobin of 8.2 gm. per cent; red cells, 2.94 million per cu. mm.; hematocrit, 26 per cent; red cell indices, M.C.V. 89, M.C.H. 28, M.C.H.C. 31; white cells, 18,300 with 73 per cent neutrophils, 6 per cent band forms, 17 per cent lymphocytes and 4 per cent eosinophils; platelets, 396,000 per cu. mm.; reticulocytes, 10.4 per cent. Slight anisocytosis and hypochromia of the erythrocytes were present. There were no spherocytes and the red cell fragility values were normal. Sedimentation rate was 138 mm. in the first hour. Sickling, not present on direct smear, was demonstrated using sodium metabisulfite. The serum iron level was 55 gamma per cent, with a total iron-binding capacity of 175 gamma per cent. No abnormal pigments were present in the plasma. The serum bilirubin determinations were normal. The Frei and Kahn tests were negative, as were agglutinin studies for enteric pathogens. The patient was group O, Rh negative (cde/cde).

The bone marrow aspirate was hypercellular with slight normoblastic hyperplasia. The myeloid: erythroid ratio was 1.8:1.0.

The direct Coombs reaction was 3+.† The serum contained anti-D and anti-E presumably due to isoimmunization by previous transfusions, and also a panantibody. In addition, another antibody identified as anti-e was demonstrated. This represented a specific autoantibody[2] as the patient was cde/cde. The cold agglutinin titer was 1:4.

The stool was grossly bloody. No ova or parasites were present. Urinalysis was essentially negative.

Sigmoidoscopy revealed a granular mucosa with a hemorrhagic, purulent exudate. Narrowing and pseudopolyp formation of the distal transverse and the descending colon were demonstrated by barium enema.

Treatment consisted of antibiotics, followed by five weeks of cortisone and then ACTH intravenously. On hormonal therapy gross blood disappeared from the stools and the guaiac reaction decreased in intensity to 1+, the hemoglobin level remained constant at 7.5 to 8.5 gm. per cent without transfusions, and the reticulocyte level decreased to 1 to 2 per cent. However, due to clinical deterioration ileostomy and subtotal colectomy were performed following three transfusions which elevated the hemoglobin to 11.9 gm. per cent. The subsequent course was uneventful.

The patient has done well since her discharge from the hospital. The ileostomy functions properly and the drainage contains no occult blood; the ileostomy fecal urobilinogen value is 2 mg. daily. Her most

† Positive direct Coombs reactions are graded in intensity from ± to 4+.

* From The Departments of Hematology and Medicine, The Mount Sinai Hospital, New York, N. Y. Aided by grants from the A. A. List, Anna Ruth Lowenberg and Jacqueline Grey Funds.

recent blood count (August 1954) was: hemoglobin, 12.1 gm. per cent; red cells, 4.39 million per cu. mm.; hematocrit, 38 per cent; red cell indices, M.C.V. 87, M.C.H. 27, M.C.H.C. 32; reticulocytes, 0.8 per cent; platelets, 240,000 per cu. mm.; white cells, 9,000 per cu. mm. with 44 per cent neutrophils, 3 per cent band forms, 41 per cent lymphocytes, 5 per cent monocytes and 7 per cent eosinophils. The direct Coombs reaction was weaker than noted previously. The antibodies in the serum were unchanged.

Comment. Active intestinal bleeding was present when the positive direct Coombs reaction was first noted, making it difficult to assess the respective roles of these two factors in production of the anemia and reticulocytosis. Due to severe bloody diarrhea and the small amount of feces in the rectal discharges, it was not feasible to determine the fecal urobilinogen prior to ileostomy. Active blood loss precluded a cell survival study. Therefore, reliance was placed on less definitive laboratory studies in attempting to decide whether significant hemolysis was occurring. The hypochromia and low serum iron level reflected the chronic blood loss and, to some extent perhaps, the chronic infection. Absence of methemalbumin, the normal serum bilirubin, low serum iron and absence of spherocytes argued somewhat against active hemolysis. The fall in reticulocytes from 10 per cent to 1 to 2 per cent on hormone therapy was also accompanied by a decrease in the occult blood in the stool from 4+ to 1+. Thus it was difficult to decide whether maintenance of the hemoglobin level was due to an effect by the hormones on a hemolytic process or on the colitis resulting in decreased blood loss. Postoperatively, with no specific therapy, and with a reticulocyte level of 1 to 2 per cent, the patient has had no drop in hemoglobin. If hemolysis had been active at that low reticulocyte level, one would have expected a marked fall in hemoglobin. Therefore, although the patient's red blood cells gave, and continue to give, a positive direct Coombs reaction, the hemolytic process probably did not contribute significantly to the anemia.

Case II. Mrs. L. P. (No. 7148), a forty-four year old housewife, was first admitted to The Mount Sinai Hospital in March, 1953, with a ten-month history of abdominal cramps, bloody diarrhea and a weight loss of thirty pounds. Physical examination was unremarkable. The diagnosis of ulcerative colitis was established by barium enema studies in conjunction with the clinical and laboratory findings, which included a hypochromic anemia and 1.2 per cent reticulocytes. The patient improved on antibiotics, ACTH and transfusions, and was discharged after a four-month hospital stay. At the time of discharge the stools were no longer grossly bloody but gave a 4+ guaiac reaction. During the following six months the colitis was in remission. The patient was rehospitalized in December, 1953, because of pain in the right upper abdominal quadrant, accompanied by emesis of bile-stained material and frequent watery, bloody, bowel movements.

On physical examination she appeared chronically ill. There was no icterus. A poorly defined tender mass in the right upper abdominal quadrant was present. The liver edge was palpable 3 cm. below the costal margin.

Examination of the blood revealed a hemoglobin of 13.9 gm. per cent and a white count of 17,400 per cu. mm. with moderate eosinophilia. A blood film showed mild hypochromia and toxic granulation. No spherocytes were present and the red cell fragilities were normal. The sedimentation rate was 67 mm. in the first hour. Abnormal pigments were absent from the plasma and the serum bilirubin values were normal. The fecal urobilinogen excretion was 10 mg. daily, consistent with the low values seen in severe diarrheal states. The patient's blood group was B, Rh positive (CDe/cde).

The bone marrow aspirate was hypercellular with 10 per cent eosinophilic myelocytes, and a myeloid: erythroid ratio of 6:1.

A 1+ direct Coombs test was noted. The serum contained a panantibody active against red cells treated with trypsin and ficin. The cold agglutinin titer was 1:4.

The gallbladder failed to visualize after a double dose of radiopaque material. By barium enema shortening of the colon with multiple areas of ulceration and small filling defects were demonstrated, the entire colon being involved except for the cecum and proximal ascending colon. Sigmoidoscopy revealed an edematous, profusely bleeding mucosa which on biopsy showed eosinophilic infiltration without arteritis.

The stools were grossly bloody, contained no ova or parasites. A trichinella skin test was negative. Agglutinin studies for enteric bacteria were also negative.

Shortly after admission symptoms in the right upper quadrant subsided. However, the patient continued to have as many as eight liquid, bloody bowel movements daily. In three weeks the hemoglobin fell to 9.0 gm. per cent, with a red cell count of 3.5 million per cu. mm.; hematocrit, 29 per cent; reticulocytes, 2.0 per cent; red cell indices, M.C.V. 82, M.C.H. 26, and M.C.H.C. 31; platelets, 274,000 per cu. mm.; and white cells, 9,400 per cu. mm. with 46 per cent neutrophils, 20 per cent band forms, 7 per cent eosinophils, 24 per cent lymphocytes and 3 per cent monocytes.

During the following months the patient received six transfusions, and for seven weeks was treated with antibiotics and symptomatic measures without improvement. ACTH gel was then administered for five weeks, followed by maintenance cortisone therapy. With hormonal therapy alone the hemoglobin level was maintained at 11 gm. per cent, with 2 per cent reticulocytes. Repeat sigmoidoscopy showed

decreased inflammatory changes in the mucosa. The patient was subjectively improved and was having fewer stools with only small amounts of gross blood when discharged in April, 1954. On hormonal therapy it was noted that although there was no change in the intensity of the direct Coombs reaction, the panantibody in the serum was no longer demonstrable.

Comment. As in Case I, this patient had intestinal bleeding at the time of discovery of the positive Coombs test. While hospitalized, the rectal bleeding became very marked and, consistent with this, the hemoglobin level fell. A 2.0 per cent reticulocytosis was present. The normal bilirubin level, and absence of marked reticulocytosis, methemalbumin, spherocytosis and erythroid hyperplasia of the bone marrow were points against a marked hemolytic process. The low fecal urobilinogen value was inconclusive in the presence of severe diarrhea. A red cell survival study could not be undertaken, due to persistent rectal bleeding. On hormonal therapy the intestinal bleeding decreased and, following transfusions, the hemoglobin was maintained at a constant level of 11.0 gm. per cent with low grade reticulocytosis. It is therefore impossible to state definitely whether maintenance of the hemoglobin level was due to an effect on a hemolytic process or directly on the colitis. However, the consensus was that probably no significant hemolysis was occurring in this patient whose direct Coombs reaction was only 1+ in intensity.

CASE III. Mrs. F. L. (No. 5075), a forty-four year old housewife, first became ill in 1937 when, at age twenty-seven, she noted abdominal cramps and frequent, bloody, bowel movements. Since then she has had several remissions and exacerbations, with hospitalizations in 1941 and 1946 during which the diagnosis of ulcerative colitis was corroborated by sigmoidoscopy and barium enema. Physical examination had been essentially negative. Treatment had been symptomatic. Two blood transfusions had been administered in 1941, and two in 1946, all without incident.

In December, 1948, while her colitis was quiescent, jaundice accompanied by severe anemia was noted. She received iron and two blood transfusions during the following seven months. The colitis remained inactive. However, in July, 1949, she was hospitalized because of thrombophlebitis, which subsided shortly after admission.

On physical examination the patient appeared acutely ill, pale and icteric. The liver and spleen were non-tender and enlarged to 2 cm. below their respective costal margins. The left calf was warm and tender, with edema of the ankle and a positive Homans' sign.

Blood examination revealed a hemoglobin of 6.0 gm. per cent; red cells, 1.65 million per cu. mm.; hematocrit, 18 per cent; reticulocytes, 72 per cent; red cell indices M.C.V. 113, M.C.H. 37, M.C.H.C. 33; platelets, 254,000 per cu. mm.; white cells, 12,000 per cu. mm. with 65 per cent neutrophils, 17 per cent band forms, 13 per cent lymphocytes, 2 per cent monocytes and 3 per cent myelocytes. One hundred thirty nucleated red cells per 100 white cells were present. The smear contained numerous spherocytes and polychromatophilic cells, marked basophilic stippling, and showed anisocytosis and poikilocytosis of the erythrocytes. Osmotic fragility was greatly increased. Hemolysis began at 0.72 per cent NaCl and was complete at 0.32 per cent NaCl.

The bone marrow aspirate was hypercellular, 75 per cent of all the cells being erythroid precursors.

The patient's blood group was B, Rh positive (CDe/CDe). The direct Coombs reaction was 4+. The serum contained a panantibody and anti-E, presumably due to isoimmunization by previous transfusions. The cold agglutinin titer was 1:8.

A red cell survival study using the modified Ashby technic revealed that 65 per cent of the transfused cells were destroyed in four days.

The indirect serum bilirubin was 2.9 mg. per cent. The direct van den Bergh reaction was positive, the prothrombin time was 18 seconds, control 12.5 seconds. Other laboratory findings including urinalysis and stool examination were normal.

At the time of hospital admission the patient's stools were formed and guaiac-negative. Aureomycin was administered for a short period, with recurrence of bloody diarrhea which persisted for almost the entire hospital stay. Over a three-week period the patient received 5,500 cc. of blood. Splenectomy was performed, followed by uneventful recovery. The spleen weighed 450 gm. and showed "active hyperemia as seen in hemolytic anemia."

One month postsplenectomy her hemoglobin was 10.1 gm. per cent, with 10 per cent reticulocytes, and the bilirubin level was normal. The fecal urobilinogen excretion was 246 mg. daily. She was discharged improved six weeks following surgery, still showing some occult blood in the stools.

She was well until March, 1953, when following an upper respiratory infection she was rehospitalized because of exacerbation of colitis. The hemoglobin was 12.4 gm. per cent. The direct Coombs test was 3+, the serum antibody content was unchanged. Sigmoidoscopy revealed ulceration and polypoid changes of the mucosa. Because of this and the recurrent activity of the disease, ileostomy and subtotal colectomy were performed.

Following discharge she improved, until July, 1953, when serum hepatitis developed, characterized by weakness, icterus and a tender liver enlarged to 6 cm. below the costal margin. The serum bilirubin level was 4.9 mg. per cent, chiefly direct reacting, and the cephalin flocculation test was three plus. She recovered with standard medical therapy. Hemoglobin was maintained at 12.5 gm. per cent throughout the entire period.

Her most recent admission to The Mount Sinai Hospital was in February, 1954, for a discharging

sinus tract opening on the abdominal wall. Physical examination also revealed a small incisional hernia, a rectal stricture and a well functioning ileostomy. The liver was not palpable.

The blood findings were: hemoglobin, 13.0 gm. per cent; red cells, 4.82 million per cu. mm.; hematocrit, 43 per cent; red cell indices, M.C.V. 89, M.C.H. 29, M.C.H.C. 32; white cells, 8,900 per cu. mm. with 43 per cent neutrophils, 8 per cent band forms, 41 per cent lymphocytes, 1 per cent eosinophils, and 7 per cent monocytes; platelets, 352,000 per cu. mm.; reticulocytes, 1.6 per cent. No spherocytes were present and the red cell fragilities were normal. No methemalbumin was present in the plasma. The urine urobilinogen excretion was less than 1 mg. daily. Neither urobilinogen nor occult blood was present in the ileostomy drainage. The bone marrow aspirate was normally cellular with a myeloid:erythroid ratio of 3:1. The direct Coombs reaction was only 1+. The panantibody and anti-E were still demonstrable in the serum. Blood chemical determinations were normal.

On March 1, 1954, an abdominoperineal resection was performed from which the patient made an excellent recovery. The pathologic report of the specimen was "acute and chronic ulcerative colitis with areas of atrophy and repair."

Summary and Comment. The seventeen-year course of this patient's ulcerative colitis has ranged the entire gamut of complications and management, with several remissions and exacerbations on medical therapy, finally requiring ileostomy and subtotal colectomy with subsequent abdominoperineal resection at age forty-three. During a two-year remission of colitis a severe autoimmune hemolytic process developed characterized by icterus, splenomegaly, severe anemia, extreme reticulocytosis, spherocytosis and a 4+ direct Coombs reaction, accompanied by pan- and iso-antibodies in the serum. Splenectomy was performed. At the present time, five years following splenectomy, most of the laboratory findings have reverted to normal except that the patient's red cells yield a one-plus direct Coombs reaction and the antibodies in the serum persist.

In contrast to the previous two cases there is no doubt in this instance about the genesis of the anemia which was present at the time the positive direct Coombs test was noted. The patient had been in clinical remission from her ulcerative colitis for more than two years and her stools were negative for occult blood when the 4+ direct Coombs reaction was noted. Therefore, blood loss could not be implicated as the cause of the severe anemia. The physical findings and laboratory data, including cell survival studies, indicated the presence of a severe autoimmune hemolytic process for which splenectomy was performed. Subsequently, due to reactivation of the colitis, ileostomy, subtotal colectomy and abdominoperineal resection were carried out. Following these surgical procedures the patient has been maintaining her hemoglobin at a high level and has normal laboratory findings except for the presence of antibodies in the serum and a 1+ direct Coombs reaction, despite which the hemolytic process has apparently subsided.

Case IV. Mrs. L. B. (No. 26168) was first admitted in June 1951, at age seventeen, with a six-month history of mucous diarrhea, abdominal cramps and moderate fever. She had been treated symptomatically by her physician. Three months prior to admission migratory polyarthritis and erythema nodosum developed. At no time was gross blood noted in her stools. Despite this a normochromic anemia developed which was unresponsive to liver and iron therapy, and in May, 1951, the patient received one transfusion at another hospital. She continued to have about eight liquid bowel movements daily, and the following month was admitted to The Mount Sinai Hospital for the first time.

Physical examination revealed moderate wasting and pallor. There was no icterus. Other than a temperature of 101°F. the positive findings were confined to limitation of extension of both elbows, external hemorrhoids and the lesions of erythema nodosum on both legs.

Blood examination revealed a hemoglobin of 10.8 gm. per cent; red cells, 3.73 million per cu. mm.; hematocrit, 33 per cent; red cell indices, M.C.V. 88. M.C.H. 29, M.C.H.C. 33; white cells, 7,700 per cu. mm. with 29 per cent neutrophils, 49 per cent band forms, 18 per cent lymphocytes, 2 per cent eosinophils and 6 per cent monocytes; platelets, 300,000 per cu. mm.; reticulocytes, 0.8 per cent. The red cells were normochromic with slight anisocytosis and poikilocytosis, perhaps a reflection of the previous transfusion. No spherocytes were noted. The sedimentation rate was 82 mm. in the first hour. Urinalysis was normal. The stools were semiliquid, without gross blood, and gave either negative or 1+ reactions to guaiac reagent. Repeated examinations were negative for ova and parasites. Blood chemistry examinations including direct and indirect bilirubin were normal.

On admission, barium enema revealed diffuse changes of ulcerative colitis involving the entire colon, except for the rectum, which was also normal on proctoscopic examination.

Four weeks of therapy with intravenous ACTH resulted in disappearance of fever and erythema nodosum, a slight decrease in the frequency of bowel movements and accompanying well-being. Cessation of therapy resulted in reversion to the pretreatment state. Cortisone was then administered for six weeks, again with resultant improvement which was not maintained following cessation of therapy.

Surgical intervention was suggested in October, 1951, when a repeat barium enema failed to demonstrate improvement and proctoscopy revealed a friable, ulcerated anal mucosa. Ileostomy and subtotal colectomy were performed, prior to and during which 1,500 cc. of blood were administered. The

postoperative course was uneventful. The pathologic report was " . . . severe acute and chronic ulcerative colitis with a similar . . . milder process in the dissected segment of ileum." On discharge from the hospital the hemoglobin was 12.6 gm. per cent.

Thereafter the patient did well and gained thirty pounds in weight. However, in July, 1953, small amounts of blood and mucus were passed from the colostomy stump and rectum. This persisted for the following thirteen months and on August 2, 1954, she was readmitted for an abdominoperineal resection.

On physical examination the patient was in no distress and was not icteric. The ileostomy functioned properly. A small draining colostomy opening and two perineal fistulas were present.

Blood examination revealed a hemoglobin of 12.4 gm. per cent and a white count of 11,800 per cu. mm. with a normal differential. Urinalysis was normal and the ileostomy drainage contained no occult blood. Blood chemical determinations including direct and indirect bilirubin were normal. Proctoscopy revealed the anal mucosa to be very edematous and friable.

Due to difficulty in cross-matching blood for the projected surgery, detailed antibody studies were undertaken. The patient's blood group was B, Rh positive (CDe/cde), the direct Coombs test was weakly (±) but definitely positive. The serum contained an anti-E and a panantibody, both revealed only by ficin-treated red cells, and an anti-Kell, present to 1:256 titer. No cold agglutinin was present. The bone marrow was normally cellular with a myeloid:erythroid ratio of 3:1.

An abdominoperineal resection was performed, during and following which 1,500 cc. of blood were administered. The postoperative course was uneventful. Pathologic report of the specimen was chronic ulcerative colitis with areas of atrophy, scarring and hemorrhage. A postoperative blood count was: hemoglobin, 12.6 gm. per cent; red cells 4.6 million per cu. mm.; hematocrit, 41 per cent; reticulocytes, 1.0 per cent; red cell indices, M.C.V. 87, M.C.H. 26, M.C.H.C. 31; platelets, 236,000 per cu. mm.; white cells, 8,800 per cu. mm. with 66 per cent neutrophils, 7 per cent band forms, 24 per cent lymphocytes and 3 per cent monocytes. The red cells were slightly hypochromic. There were no spherocytes and the red cell fragilities were normal.

Comment. Despite the lack of gross blood in her stools during the first six months of colitis, anemia developed which was unresponsive to liver and iron and for which the patient received one transfusion. No icterus, splenomegaly, spherocytosis or reticulocytosis was present but no significant amount of occult blood occurred in her stools. Thus it is possible that the anemia may have been due in part to a hemolytic process as well as to chronic infection. Unfortunately, no direct Coombs test or antibody studies were performed at the time of ileostomy and subtotal colectomy.

Almost three years later, immediately prior to an abdominoperineal resection, the patient was noted to have a positive direct Coombs test and several antibodies in the serum. Despite these findings, however, no evidence for active hemolysis was found and the patient was not anemic. She had had no transfusions or other medications since the previous hospitalization and was not troubled by colitis except for minimal bleeding for one year prior to the discovery of the positive direct Coombs test. It is therefore possible that the positive direct Coombs test may have been present three years previously at the time severe anemia was noted.

DISCUSSION

The four cases presented have in common the association of severe ulcerative colitis and a positive direct Coombs test. The patients were all women, three white and one Negro, of various blood groups (O, cde/cde; B, CDe/cde; B, CDe/CDe; B, CDe/cde). In the first three patients the Coombs reactions were of varying intensities (1+, 3+, 4+), and did not appear to be related to the age of the patients (twenty-eight, forty-five, thirty-seven years), the previous duration of the colitis (one, one and one-half, eleven years), or the extent of colonic involvement. Immediately prior to the discovery of the positive direct Coombs reaction two of the patients (Cases I and II) had had episodes of active colitis of twelve months' and three weeks' duration, respectively. However, Case III was in remission when hospitalized for a severe autoimmune hemolytic process. Case IV should probably be considered separately as the Coombs test was first performed three years following ileostomy and subtotal colectomy, rather than earlier in the course of the disease when it may first have become positive.

The patients had received a comparatively small number of transfusions (four to ten), beginning from six months to eight years prior to the discovery of the positive antiglobulin test. Subsequently, additional transfusions were administered to all four and were well tolerated.

Jaundice and hepatomegaly accompanying the globulin-coated red cells was found only in Case III, although moderate hepatic enlargement was noted in Case II. No significant lymphadenopathy was evident in any of the patients.

In Cases I and II short courses of ACTH and cortisone given primarily for their possible effect on the colitis did not result in any change in the intensity of the Coombs reaction.

The concept of an immunologic mechanism as causative in some cases of acquired hemolytic anemia, first postulated and demonstrated by Chauffard and Vincent,[3] was re-emphasized by Dameshek and Schwartz.[4] With the discovery of the antiglobulin test[5] it became possible to detect incomplete Rh agglutinins in hemolytic disease of the newborn, supposedly due to adsorption of the globulin antibodies on the surface of the red cells. The application of the Coombs test to other hemolytic processes by Boorman et al.[6] permitted differentiation of congenital spherocytosis from acquired hemolytic anemia and demonstrated that the latter was an immune process.

Although coated erythrocytes can frequently be demonstrated in acquired hemolytic anemia, the question of whether globulin-coated red cells invariably have a shortened life span has been considered by several investigators. Mollison and Paterson[7] demonstrated by cell survival studies, using Rh positive cells previously incubated with serum containing Rh antibody, that most of the sensitized red cells survived normally when transfused into anemic patients. They postulated that a certain minimal quantity of antibody was needed for hemolysis. Loutit and Mollison[8] transfused coated red cells from a patient with acquired hemolytic anemia into a normal person and found that they had a normal life span. They postulated that a co-hemolysin in the plasma may be required in addition to the hemolysin on the red cell to result in a decreased red cell life span. Selwyn and Hackett[9] followed the survival of erythrocytes by the Ashby technic and performed "differential direct Coombs counts" to distinguish sensitized and unsensitized red cells. Blood from a patient with acquired hemolytic anemia was transfused into a normal patient and it was noted that there was rapid destruction for ten to fifteen days, followed by a normal rate of destruction with a normal total life span. They too, concluded that sensitization *per se* does not necessarily mean shortened survival, and postulated that in the initial rapid destruction perhaps only the most heavily coated cells were destroyed; those less heavily sensitized surviving normally. Abnormal hemolysis may thus be a threshold phenomenon.

The activity of the hemolytic process also was thought to be related to the amount of antibody on the red cell by Evans and Duane.[10] Others,[11] however, report little if any correlation between autosensitization and autohemolysis. In the four cases with sensitized red cells herein reported hemolysis did appear to be related to the degree of sensitization. The only case with a frank hemolytic process was Case III whose direct Coombs reaction was 4+. The anemia present in the other three cases probably had no significant hemolytic component. In splenectomized patients, such as Case III, coated erythrocytes often persist even though all evidence of accelerated hemolysis has subsided.[10,12,13] In such patients[13] the spleen probably is a major hemolytic organ, although only a minor source of antibody.

Evidence has been presented that antibody formation in response to specific antigenic stimuli may occur in the reticuloendothelial system,[14] spleen,[15,16] lymph nodes[17–19] or plasma cells.[20,21]

In "idiopathic" acquired hemolytic anemia the stimulus is unknown. Viruses,[22] haptene complexes composed of a component of the red cell plus a foreign substance such as a virus or drug,[10] free fatty acids or enzymes[23] or previous transfusions, have all been implicated. It has been suggested that the action of the agent may be to modify the erythrocyte surface structure, thereby rendering it antigenic.[15] Experimentally antibody-coated red cells have been produced following repeated intraperitoneal[23] or subcutaneous[24] injection of homologous blood, which in some instances had been modified by Freund's adjuvant or by exposure of the red cells to influenza virus.

In the symptomatic hemolytic anemias the underlying condition is presumably responsible for the hemolytic process.[25–27] The mechanism may be that of direct injury of the erythrocytes or alteration of their surface structure[27] stimulating the production of autoantibodies of low specificity which affect normal red cells as well as the altered ones. In the hemolytic process often associated with the lymphomas[7,10,11,29] the tissue itself may produce abnormal autoantibodies which coat the patient's red cells.[11] In the "reticuloses" it has been postulated that "the abnormal tissues may destroy excessive numbers of red cells, and thus provoke hemolytic antibody production."[28]

In ulcerative colitis there are alterations in the absorption of fat, carbohydrates and amino acids by the small intestine.[30] It is possible that in this disease certain normally rejected substances are absorbed by the colon or by the

small intestine. These substances may possess antigenic properties in common with the erythrocytes, thus stimulating the formation of red cell antibodies. Similarly, the diseased colon itself may have a haptene in common with the erythrocytes which might stimulate the production of antibodies capable of coating the red cells.

While the mechanism of antibody elaboration is unknown, it nevertheless appears that the occurrence of positive direct Coombs reactions in ulcerative colitis is more than fortuitous and is probably related to the presence of diseased bowel although independent of the activity of the colitis. Case III had been in clinical remission from colitis for more than two years at the time the severe autoimmune hemolytic process became manifest. Although splenectomy had induced a remission in the hemolytic process, the 4+ intensity of the Coombs reaction decreased only slightly in a four-year period. Within one year after ileostomy and subtotal colectomy, however, it had decreased to 1+. Thus even though gross hemolysis had ceased with removal of the spleen, there was not much change in the amount of antibody coating the red cells until the diseased colon had been removed. In Case IV, unfortunately, no direct Coombs test was performed at the time the patient was found to have been severely anemic, despite the lack of significant amounts of occult blood in her stool and the short duration of her illness. A slightly positive direct Coombs reaction was recently noted, almost three years later. At this time the patient was no longer anemic and had no evidence of hemolysis. By analogy with Case III it is very possible that at the earlier hospital admission the patient had a strongly positive direct Coombs test which over the intervening years, subsequent to ileostomy and subtotal colectomy, diminished to its present intensity. In Case I only seven months have elapsed since ileostomy and subtotal colectomy. However, the patient now has no anemia or reticulocytosis and there has been a slight but definite diminution in the intensity of the direct Coombs reaction. If the diseased bowel plays a role in initiating or maintaining the antibody coating of the erythrocytes, with the passage of time its removal should result in a further diminution of the intensity of the direct Coombs reaction, as happened in Case III and as may have occurred in Case IV. Whether the ileostomy, with its diversion of fecal material which may contain antigenic substance that might otherwise be absorbed, or the subtotal colectomy, resulting in the removal of diseased bowel which may have haptenes in common with the erythrocytes, is the more important in causing diminution of the direct Coombs reaction cannot as yet be stated.

SUMMARY

Four cases of ulcerative colitis associated with antibody-coated red cells are presented. The clinical, hematologic and immunologic findings are discussed.

One of the patients had overt hemolytic anemia of the acquired autoimmune variety. It was not possible to assess the role played by hemolysis in the anemia presented by the other three patients.

The occurrence of antibody-coated red cells in ulcerative colitis appears to be related to the underlying intestinal disorder, and particularly to the presence of diseased bowel, although it is not necessarily related to the clinical activity of the colitis.

The possibility of an autoimmune hemolytic process should be considered in the pathogenesis of anemia in ulcerative colitis.

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Prostatic Cancer*

XII. Extremely Elevated Serum Acid Phosphatase Associated with Altered Liver Function

PERRY B. HUDSON, M.D., KENNETH K. TSUBOI, PH.D. *and* ARNOLD MITTELMAN, M.D.
New York, New York

VALUES above a statistically established upper limit for the normal acid phosphatase activity in serum are almost always indicative of metastatic adenocarcinoma of the prostate gland.[1] In such instances the source of additional enzyme present in the serum is believed to be the secretion of the prostatic acini which form the metastases; such glandular structures, having no prostatic ductile outlet comparable to the normally situated gland, pour acid phosphatase into the surrounding tissue. The enzyme, being freely diffusible, then appears in increased amounts in the blood.

Such a convenient and apparently acceptable explanation of the sequence of events which lead to an increase in the quantity of enzyme in the blood leads one to speculate about the mechanism by which acid phosphatase is eliminated or destroyed. The excretion of alkaline phosphatase in the bile seems an established fact[2] but knowledge of the fate of prostatic acid phosphatase is lacking. It has been assumed that the acid phosphatase of the urine in man is largely derived from prostatic washings by the urine and merely represents the enzyme added by the normal "resting" prostatic secretion.[3] Urinary acid phosphatase of prostatic origin is not increased by the development of metastases from prostatic cancer, even in the presence of an elevated serum level.

The present report is concerned with the coexistence of enormously increased amounts of serum acid phosphatase and extensive metastases of the liver from prostatic cancer, and with a possible cause and effect relationship. A study of this relationship in three patients will be described.

CASE REPORTS

CASE 1. C. B. (Presbyterian Hospital Unit No. 825,045), a sixty-four year old white man, was admitted to the hospital on April 12, 1946, for relief of acute urinary retention which had developed during a one year period of symptoms suggesting prostatic obstruction. No history of cardiorenal, hepatic or other systemic disease was present. A diagnosis of prostatic cancer was made by rectal palpation. Initial treatment consisted of enucleation prostatectomy, bilateral orchiectomy and commencement of daily oral dosage of 5 mg. of diethylstilbestrol. The surgical-pathologic specimen provided a confirmatory diagnosis of adenocarcinoma of the prostate gland, well differentiated. During this hospitalization neither radiographic nor serum acid phosphatase studies were indicative of metastatic disease. The patient, symptomatically improved, was discharged on June 9, 1946.

On September 24, 1951, this man was again admitted to the hospital in acute urinary retention. The rectal palpation appraisal at this time was suggestive of local extension of a neoplasm originating in the prostate gland. The serum acid phosphatase level on October 3, 1951 was 4.2 Gutman units. There was no evidence by x-ray of osteoblastic metastases. The patient was relieved of 800 cc. of residual urine and treated by continuous gravity drainage by means of an indwelling Foley bag urethral catheter. The diethylstilbestrol oral dosage was increased to 500 mg. daily. The urethral catheter was removed prior to the patient's discharge from the hospital on October 10, 1951, at which time urethral voiding was abnormal only in that

* From the Departments of Urology and Biochemistry, Francis Delafield Hospital and the Institute of Cancer Research, Columbia University College of Physicians and Surgeons, New York, New York. This study was supported by a grant from the Damon Runyon Memorial Fund.

it was frequent and characterized by a weak urinary stream.

On January 3, 1952, the patient was readmitted with a primary complaint of sudden appearance and progressive enlargement of an epigastric mass, with concomitant asthenia, anorexia and constipation. For the first time he complained of intermittent, low back pain. The lower edge of the non-tender liver was palpable 5 cm. below the right costal margin. The spleen was also found to be enlarged on palpation. There was bilateral ankle edema. Little change in observations at rectal palpation of the prostate gland was noted. The serum alkaline phosphatase level was elevated to 15.4 units (Bodansky) and the acid phosphatase to 201 units (Gutman). The cephalin flocculation test was 2+ and the thymol turbidity test 3+. The albumin:globulin ratio was 2.6:2.4. The blood urea nitrogen, sodium and potassium were within normal limits. Fourteen days after this readmission jaundice became evident, persistent dark urine and light stools developed, ascites accumulated and dependent edema increased. The alkaline phosphatase rose to 18.4 units, and the acid phosphatase to 319 units. A small area of increased density appeared on x-rays in the left side of the bony pelvis. By the twenty-fifth hospital day the patient was semicomatose, and on January 27, 1952 he died.

The significant observations noted at autopsy were confined to the lungs, liver, urinary bladder, prostate gland, the lymphatic system and the red bone marrow. In the lungs tumor cells in the lymphatics, blood vessels and lung parenchyma were present. This process was extensive. In the liver the hepatic architecture was completely destroyed. Extensive areas of necrosis and infiltration by inflammatory and tumor cells were noted. The urinary bladder was dilated and trabeculated; although inflammatory changes were present in the subepithelial layer, no invasion by neoplastic cells occurred. Large areas of necrosis in the prostatic bed with extension into the surrounding perineal and pelvic structures were present. There were some areas of well differentiated neoplastic cells. Tumor infiltration extended into the bladder neck. Lymph glands in the cervical, thoracic and abdominal regions were almost completely replaced by tumor tissue. The glandular capsules were the only remnants of the normal architectural structure. Of special interest was the bone marrow: throughout the examination of the red marrow system only one microscopic section of all those taken showed any tumor tissue whatever.

Case II. J. S. (Francis Delafield Hospital No. 2878), a seventy-seven year old white man was admitted to the Francis Delafield Hospital on May 5, 1953, for terminal care; a diagnosis of metastatic carcinoma of the prostate had been made. At another hospital a serum acid phosphatase of 16.3 Bodansky units, alkaline phosphatase 25.1 Bodansky units, albumin 3.8 gm. per cent and globulin 2.6 gm. per cent were recorded. Upon admission to the Delafield Hospital the patient was confused and disoriented. Physical signs of a left pleural effusion, confirmed by x-ray, were noted. The liver edge was palpable five fingerbreadths below the right costal margin in the mid-clavicular line; it was hard but no nodules were palpated. Jaundice was not present. The prostate was stony hard and fixed. Blood studies of May 7, 1953 revealed an acid phosphatase of 475 Bodansky units, alkaline phosphatase 24.7, serum bilirubin 0.2 mg. per cent, thymol turbidity 2.1 units, cephalin flocculation test 1+ and hemoglobin 6.5 gm. No bile was present in the urine. X-ray studies at this time showed osteoblastic and osteolytic metastases in the lumbar spine, ribs and shoulder girdle. A chest x-ray film demonstrated, in addition to a left pleural effusion, diffuse peribronchial infiltration.

Within the following week the patient was given transfusions of two liters of whole blood. Several days thereafter he became increasingly dyspneic and disoriented. Liver function tests were repeated on May 29. The thymol turbidity test was 4.5 units, cephalin flocculation test 2+, serum bilirubin 0.4 mg. per cent, bromsulfalein 14 per cent retention in forty-five minutes and prothrombin time 19.4 seconds (normal 11.4). The serum acid phosphatase was 400 Bodansky units and the alkaline phosphatase 32.3 Bodansky units. By June 2 jaundice was observed clinically and the patient became cyanotic. Digitalis was administered, mercurial diuretic drugs were given and the patient was placed in an oxygen tent. On June 3, after several convulsive seizures, he died. No autopsy was performed.

Case III. C. W. (Francis Delafield Hospital No. 3202), a fifty-two year old Negro man, a laborer, was admitted to the Francis Delafield Hospital on November 6, 1953. For five months he had complained of sacral and bilateral lower extremity pain and for three to four weeks of

generalized pruritus. At the time of the patient's admission to the hospital moderate jaundice developed but the liver was not palpable. Examination of the rectum revealed a stony hard, fixed prostate. A radiographic skeletal survey revealed widespread osteoblastic lesions. A serum acid phosphatase of 550 Bodansky units and an open perineal biopsy confirmed a diagnosis of metatastic prostatic carcinoma.

Laboratory studies during hospitalization gave the following positive results: serum bilirubin 7.5 mg. per cent, prothrombin time 18.9 seconds (normal 14.8), cephalin flocculation test 2+ and thymol turbidity test 3+. Albumin: globulin 3.3:3.4 gm. per cent and alkaline phosphatase 23.4 Bodansky units.

On December 24, 1953, under continuous caudal anesthesia, bilateral orchiectomy was performed. Immediately postoperatively the patient was given 500 mg. of diethylstilbestrol a day. Within one month he was free of pain and had gained 10 pounds. During this period the jaundice disappeared, prothrombin time returned to within normal limits, serum bilirubin was 0.4 mg. per cent, cephalin flocculation test 1+, the thymol turbidity test gave negative results, albumin:globulin was 4.1:3.4 gm. per cent, alkaline phosphatase 25.4 and acid phosphatase 1.0 Bodansky units. The patient was discharged February 1, 1954, and has continued to do well.

EXPERIMENTAL STUDIES

In spite of extensive literature concerning the elevation of acid phosphatase in the sera of patients with metastatic carcinoma of the prostate, precise identification of the enzyme (or enzymes) responsible for this elevation does not appear to have been established, although Gutman and Gutman provided evidence that it is of prostatic origin.[4] For this reason a study of the qualitative nature and the quantitative level of the acid phosphatase of various body fluids and tissues (where feasible) was made. Results of such investigations will be presented in the following sections. Source material for all the experiments listed, unless otherwise specified, was derived from the patient discussed in Case 1 (C. B.). The material was considered especially well suited for these investigations in view of the exceptionally high concentration of acid phosphatase present within the serum of this patient. Results of kinetic studies done on the sera of the other patients listed in this report were qualitatively similar to those results derived from the study of material of patient C. B. and have therefore not been included as a part of this report. The increased serum acid phosphatase observed in these patients was concluded to be, in fact, of prostatic origin on the basis of kinetic evidence which has been summarized in detail in the following sections.

Preparation of Source Materials for Enzyme Studies. The serum, in addition to being tested directly after appropriate dilution, was subjected to ammonium sulfate fractionation for further investigation. The bulk of the enzyme, representing approximately 85 per cent of the original total, was recovered between 0.63 to 0.67 saturation with ammonium sulfate (at 23°C.) in the presence of 0.1 M acetate buffer at pH 5.5. The resulting enzyme fraction was estimated to represent an approximate eightfold purification on the basis of tyrosine measurements using the reagent of Folin and Ciocalteau.[5]

Approximately 5 gm. of the primary neoplastic tissue were removed and homogenized with 9 volumes of water. It was necessary that the tissue, because of its fibrous nature, be cut into small pieces prior to homogenization. The resulting homogenate was centrifuged for ten minutes at 23,000 × g. The sediment was found to contain no enzyme and was discarded. The remaining supernate was used for the enzyme measurements.

Approximately 5 gm. of hepatic metastatic tissue were selected and removed. The tissue was homogenized with 9 volumes of water and used directly for the enzyme measurements.

Approximately 2.5 gm. of the osseous metastases were selected and removed. The tissue was thoroughly pulverized and ground with a mortar and pestle, after which 9 volumes of water were added. The resulting suspension contained no gross bone fragments. It was lightly centrifuged (2,500 × g for ten minutes) and the resulting supernate was taken for the enzyme measurements.

The urine sample (235 ml.) was tested directly for enzyme.

Enzyme Measurements. Reliable methods for the accurate measure of prostatic acid phosphatase using various substrates were previously developed in connection with other investigations and have been applied in these studies. Only a brief description of the methods will be presented. The methods as applied have incorporated optimum conditions for enzymatic

activity with respect to substrate concentrations (that is, saturating levels in each instance), hydrogen ion concentration and incubation time. All assays were done on at least two levels of enzyme concentration to insure strict proportionality between enzyme concentration and activity.

Commercial preparations of phenylphosphate, beta-glycerophosphate and yeast adenylate of high purity served as enzyme substrates in the differential study. Details concerning purification procedures and relative purity of each substrate have been presented elsewhere in connection with other studies.[6] Each of the substrates was prepared at high concentrations and adjusted to appropriate hydrogen ion concentration prior to use (due to inherent buffering properties).

Stock solutions of molar acetate buffer were prepared to cover the pH range from 4.0 to 6.0 and were used at a final 0.1 M concentration within the reaction mixtures.

All enzyme measurements were carried out in a final 1 ml. reaction volume. Larger volumes were avoided in order to maintain high concentrations of substrate (that is, saturating levels) while limiting the absolute quantities within the reaction mixtures. The presence in excess of a specific amount of two of the three substrates (beta-glycerophosphate and yeast adenylate) was found to interfere markedly with the colorimetric determination of inorganic phosphorus.[6] Tubes were prepared in advance containing substrate, buffer and water (if required) to 0.5 ml. volume. To the prepared tubes 0.5 ml. volume of appropriately diluted enzyme solution was added. The reaction tubes were incubated at 37°c. for a thirty and sixty minute period to insure strict proportionality between incubation time and enzyme activity with each new sample investigated. Following the incubation period, the reaction was stopped by the addition of 5 ml. 10 per cent trichloroacetic acid. The contents of the tubes were filtered (if required) through acid-washed paper and aliquots of the filtrate removed for inorganic phosphorus determination.[7]

RESULTS

Serum Studies. The marked elevation of serum acid phosphatase found on routine laboratory study was readily confirmed. Table 1 summarizes the measurements of the acid phosphatase activity on the serum. The enzyme was tested at three dilutions in the presence of saturating levels of three separate substrates. The reliability of the assay methods is demonstrated by the strict proportionality obtained between enzyme concentration and activity in each of the substrates used. All enzyme assays were made at pH 5.5 in 0.1 M acetate buffer after preliminary experiments had indicated such an acidity to be most nearly the average optimum for the three substrates (each substrate showing a slightly different pH optimum). A measure of the serum for acid phosphatase activity under optimal (or near optimal) conditions showed hydrolysis of 1250 mg. P per hour per 100 ml. serum using saturating levels of phenylphosphate. The hydrolysis of 1250 mg. P corresponds to the simultaneous release of 3790 mg. phenol. From the clinical report, 319 mg. phenol were calculated to have been hydrolyzed per hour per 100 ml. serum by using the assay procedure of Gutman and Gutman,[8] approximately twelve times less than observed by our methods; the discrepancy between the two levels is undoubtedly the result of improper dilution in the initial assay with a consequent error in this unusually high range of values.

TABLE 1

QUANTITATIVE MEASURE OF ACID PHOSPHATASE ACTIVITY ON THREE DIFFERENT SUBSTRATES WITHIN THE SERUM SAMPLE UNDER INVESTIGATION

Dilution of Serum*	Substrate†		Phosphorus Liberated/hr. at pH 5.5‡		
	Compound	Concentration (molar)	Per Reaction Vessel (μg)	Per ml. Serum (calculated) (mg.)	Per 100 ml. Serum (calculated) (mg.)
1:500	Phenylphosphate	0.138	12.4	12.4	1240
1:250			25.3	12.7	1270
1:125			49.6	12.4	1240
1:500	β-glycerophosphate	0.128	13.6	13.6	1360
1:250			27.2	13.6	1360
1:125			52.0	13.0	1300
1:500	Yeast adenylate	0.066	10.1	10.1	1010
1:250			20.9	10.5	1050
1:125			41.2	10.3	1030

* Dilutions made in distilled water; to the reaction mixtures was added 0.5 ml. of the diluted serum for enzyme measurements.

† Substrates were prepared as concentrated stock solutions adjusted to pH 5.5. To the reaction mixtures was added 0.2 ml. of 0.69 molar phenylphosphate, 0.2 ml. of 0.64 molar beta-glycerophosphate and 0.3 ml. of 0.22 molar yeast adenylate, respectively. The concentrations of substrate used represent saturating levels in each instance.

‡ Phosphorus released by enzyme cleavage (that is, in excess of that contributed as contaminants by the substrates and serum) was determined after one hour incubation at 37°c. in the presence of 0.1 molar acetate at pH 5.5. All final reaction volumes were 1 ml.

The serum acid phosphatase was found to hydrolyze beta-glycerophosphate at a rate comparable to that observed with phenylphosphate. The action of the enzyme on yeast adenylate was somewhat less than that observed with the other two substrates tested. The pattern of action

TABLE II
COMPARATIVE ACTION OF PROSTATIC ACID PHOSPHATASE IN PRESENCE OF SATURATING LEVELS OF PHENYLPHOSPHATE, BETA-GLYCEROPHOSPHATE AND YEAST ADENYLATE

Enzyme Preparation*	Substrate†		Acid Phosphatase Activity‡
	Compound	Concentration	
Crude prostate homogenate	Phenylphosphate	0.138 M	43.0
	β-glycerophosphate	0.128	45.2
	Yeast adenylate	0.066	37.4
Partially purified prostatic acid phosphatase	Phenylphosphate	0.138 M	404
	β-glycerophosphate	0.128	412
	Yeast adenylate	0.066	370

* Crude homogenate prepared from benign hypertrophic prostate gland by grinding finely sliced pieces in a glass homogenizer. Partial purification of the enzyme (approximately tenfold on the basis of nitrogen) accomplished by ammonium sulfate fractionation and dialysis of crude homogenate.

† Substrate concentrations represent saturating levels in each instance.

‡ Acid phosphatase activity refers to mg. P hydrolyzed/hr./mg. N at pH 5.5 and 37°c.

of the serum enzyme on each of the substrates was found to be identical with that observed with an acid phosphatase obtained from prostatic tissue. For purposes of comparison a typical measure of prostatic acid phosphatase using crude and partially purified enzyme preparations is presented in Table II. A tentative identification of the serum acid phosphatase as being in fact of prostatic origin was made on the basis of this evidence.

Further Studies on Serum Acid Phosphatase Following Partial Purification. A partial purification of the serum acid phosphatase was accomplished by ammonium sulfate fractionation, approximately eightfold on the basis of nitrogen content. The resulting enzyme preparation was subjected to intensive characterization with respect to its kinetic properties. The details concerning these investigations will be presented elsewhere[9] and only a brief summary of the results will be presented here.

The serum enzyme was found to be identical with the prostatic acid phophatase in its relationship between reaction velocity and substrate concentration, hydrogen ion and specific inhibitors (including fluoride and tartrate). Perhaps the most convincing evidence for the identity of the two enzymes is furnished by the observed action on the three separate substrates (phenylphosphate, beta-glycerophosphate and yeast adenylate). From the substrate studies the dissociation constants (K_s) for each of the substrate-enzyme complexes were determined. The K_s values for the serum enzyme were as follows: for phenylphosphate, 3 by 10^{-4} M; for beta-glycerophosphate, 4 by 10^{-3} M; and for yeast adenylate, 3 by 10^{-4} M. These values do not differ greatly from those with highly purified preparations of acid phosphatase (approximately three hundred fold based on nitrogen) from prostatic tissue.[10] Positive identification of the serum enzyme as being of prostatic origin would appear to be convincingly established on the basis of this experimental evidence.

Acid Phosphatase Composition of Primary Prostatic Neoplasm, Hepatic and Osseous Metastases and Urine. Additional investigations were carried out on postmortem material to determine the quantitative as well as qualitative distribution of acid phosphatase within different tissues. In Table III are summarized the results of the acid phosphatase measurements. The pattern of action of the enzyme associated with each of the samples of material tested strongly implicates the acid phosphatase to be of prostatic origin in each instance. Among the tissues investigated, the hepatic metastasis was found to contain the greatest concentration of enzyme. The primary prostatic neoplasm contained the least. The primary tumor was found to contain less than 3 per cent of the acid phosphatase present in a sample of non-neoplastic prostate. (Compare with results summarized in Table II.) No significance can be attached to the relative values of prostatic acid phosphatase for the metastatic tissue analyzed.

Additional experiments were performed on normal human liver for purposes of comparison with hepatic metastasis. Normal human liver was found to contain an acid phosphatase of distinctly dissimilar kinetic properties and in concentrations (assuming activity to be representative of concentration) of less than 4 per cent of the enzyme found to be present within the metastatic tissue. Studies concerning the specific kinetic properties of human liver acid phosphatase will be presented elsewhere in relation to other investigations which are prompted by liver acid phosphatase studies

reported by Davies[11] and by Bamann and Riedel.[12]

COMMENTS

The differential substrate experiments here described were considered to establish beyond any reasonable doubt that the enzyme found in the body fluids and tissues was of prostatic glandular origin. Hepatic metastases of prostatic origin of recognizable degree are uncommon. Extensive involvement of the liver by prostatic cancer such as described here is rare.

The total volume of metastatic glandular tissue in Case I is less than that in many other instances of prostatic cancer in which extremely high serum acid phosphatase levels are not detected at any time during the course of the disease. The clinical and laboratory evidence of progressive hepatic insufficiency in Case I directly paralleled the sharply rising serum acid phosphatase. In Case II the rapid fall of serum acid phosphatase following bilateral orchiectomy was accompanied by a return to normal reactions of the liver function tests. Although it cannot be stated unequivocally that patient J. S. (Case II) had extensive metastatic involvement of the liver, the presumptive evidence for hepatic spread is strong.

There are at least two possible explanations for the high level of acid phosphatase in the sera of these patients. It is conceivable that prostatic carcinoma cells in an extremely vascular organ such as the liver can more easily secrete acid phosphatase into the systemic circulation. On the other hand those unknown metabolic processes concerned with the destruction of acid phosphatase may be impaired. It is probable that the liver is in some way responsible for the catabolism of serum acid phosphatase and that injury to this organ may impair this function.

TABLE III

DISTRIBUTION OF ACID PHOSPHATASE WITHIN PRIMARY NEOPLASM, HEPATIC AND OSSEOUS METASTASIS AND URINE SPECIMEN

Additional Material Investigated	Substrate*		Mg. N per† gm. Wet Weight Material	Mg. P Hydrolyzed/hr. at pH 5.5‡		
	Nature	Conc.		Per ml. Sample	Per gm. Wet Weight Material	Per mg. Nitrogen
Primary prostatic neoplasm	Phenylphosphate	0.138M	8.3	....	81.6	0.98
	β-glycerophosphate	0.128	....	....	82.0	0.99
	Yeast adenylate	0.066	....	....	68.1	0.82
Hepatic metastasis	Phenylphosphate	0.138 M	20.7	....	333	16.1
	β-glycerophosphate	0.128	....	....	331	15.9
	Yeast adenylate	0.066	....	....	260	12.6
Osseous metastasis	Phenylphosphate	0.138 M	9.6	....	18.0	1.88
	β-glycerophosphate	0.128	....	....	16.4	1.71
	Yeast adenylate	0.066	....	....	15.1	1.57
Urine specimen	Phenylphosphate	0.138 M	....	4.64	....	....
	β-glycerophosphate	0.128	....	4.40	....	....
	Yeast adenylate	0.066	....	4.16	....	....

* Substrate concentrations represented saturating levels in each instance.

† Nitrogen was determined by micro-Kjeldahl.

‡ The reaction mixtures contained, in addition to tissue and substrate, 0.1 ml. molar acetate buffer at pH 5.5; all in a final 1 ml. reaction volume.

SUMMARY

1. The clinical and laboratory course of three patients with metastatic prostatic carcinoma and impaired hepatic function is described. In each instance there was an extremely elevated level of serum acid phosphatase activity.

2. The acid phosphatase measured in these studies was shown to be of prostatic origin.

3. In Case I the rise in serum acid phosphatase paralleled the increase in hepatic damage.

4. Case III demonstrated a parallelism between the fall of acid phosphatase after hormonal therapy and a return of liver function to normal.

5. The liver appears to be implicated in the metabolism of serum acid phosphatase of prostatic origin.

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Review

Melanin Pigmentation*

AARON B. LERNER, M.D.
New Haven, Connecticut

With increased knowledge of the cytology of melanocytes, and of the enzymic, hormonal and neurogenic factors controlling their activity, it has become possible to formulate a unified concept of melanin pigmentation in man. In the presentation of this concept, basic cytologic and biochemical factors will first be considered and this will be followed by a description of common variations in pigmentation, including changes from birth to old age.

1. Cytology of Melanocytes. Melanin is formed in the cytoplasm of melanocytes by oxidation of the amino acid tyrosine in the presence of the enzyme tyrosinase. The term clear cell refers to the perikaryon of the melanocyte. The immature pigment cell is known as a melanoblast and the non-specific macrophage which phagocytizes melanin as a melanophage. Benign proliferation of melanocytes results in formation of a nevus. Malignant proliferation of melanocytes produces a melanoma.

In general, melanocytes are believed to arise embryologically from the neural crest,[1,2] although there are still a few adherents to the theory of epithelial origin.[3] Melanocytes are present in the skin, eyes and leptomeninges. Several technics can be used to visualize these cells. They may be stained with silver, gold or methylene blue, or visualized histochemically following incubation in solutions of tyrosine or dopa.[4,5] Tyrosinase, present in the cytoplasm of most melanocytes, catalyzes the oxidation of tyrosine or dopa to the dark pigment melanin. This process is called the tyrosine reaction or dopa reaction depending upon whether tyrosine or dopa is used as the substrate.

Although the melanocytes of skin, eyes and leptomeninges probably are derived from the neural crest, these cells differ from one another in several respects. Furthermore, within one structure, such as the skin, the melanocytes at the epidermal-dermal junction differ from those in the hair bulb or dermis. Usually, although there are many exceptions, the color of skin, hair, eyes and leptomeninges is related; a person with dark skin has dark hair, eyes and leptomeninges, whereas the fair-skinned person has light hair, eyes and leptomeninges.

In skin, melanocytes are present in the basal layer of the epidermis at its junction with the dermis and in the hair bulbs. These cells have numerous dendritic processes. Melanocytes may occur in the dermis as dermal nevi. Basal layer melanocytes are not distributed uniformly over the body. More are found in the upper portions, on the face and forehead and behind the ears, than in the lower regions such as the thighs.[4,6] The palms also have relatively few pigment cells. Different races, such as Caucasian and Negro, have the same number of melanocytes in any particular location although their activity varies. With the exception of melanocytes from albinos or from depigmented areas of patients with vitiligo, skin melanocytes give a positive dopa reaction. The latter is increased when skin is treated by any method which increases the formation of melanin, for example, ultraviolet light radiation. Melanocytes from normal skin give a negative or weak tyrosine reaction.[6,7] However, exposure of skin to ultraviolet light modifies the melanocytes so that a positive tyrosine reaction can be obtained. Most nevi arise from basal layer melanocytes. Melanomas arise from melanocytes in apparently normal skin or from those in nevi. These tumors are highly malignant and metastasize widely.

Melanocytes of the hair bulb differ from those of adjacent skin in being more or less active. For example, dark hair often grows out of very light skin. In this case the melanocytes of the hair bulb are active and those in the skin are

* From the Section of Dermatology, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut.

relatively inactive. When a patient with vitiligo who is being treated with psoralen compounds is exposed to ultraviolet light, repigmentation is seen first about the hair follicles.[8] Gradually, the pigmented portions of adjacent follicular openings enlarge and coalesce. On the other hand, gray hairs may protrude from dark skin. Here the skin melanocytes are more active than those from the hair. It is possible that the differences between melanocytes of the skin and hair bulb cells are due to the influence of surrounding structures. Grafting experiments show that removal of the epidermis and upper dermis but allowing the hair bulb cells to remain intact results (after healing) in normally pigmented skin.[4] Hence, basal layer melanocytes arise from hair bulb cells. On the other hand, when superficial epidermis is removed from an area of white hair in a guinea pig and replaced by basal layer epidermal cells from an area of pigmented skin, many new hairs grow out black instead of white.[4] In this case the hair becomes pigmented by the new melanocytes.

So far as is known, melanomas are not derived from hair bulb cells. However, this is a difficult point to study because a melanoma that did arise from a hair bulb might in its early stages of development look like a pigmented nevus on the skin surface.

In the eye, melanocytes normally occur along the uveal tract and in the retina. The cells of the uveal tract are similar to those of the skin in that thay have many dendritic processes. However, it is thought that melanocytes of chick and rabbit eyes differ from those of skin by giving a positive dopa reaction before birth but a negative reaction after birth.[9] These findings are not in accord with the fact that the human eye darkens with age, thus indicating the formation of new pigment. Beef ciliary bodies probably give positive dopa and tyrosine reactions because extracts from this tissue readily catalyze oxidation of tyrosine and dopa to melanin.[9] In fish and possibly in human beings sectioning sympathetic fibers results in hyperpigmentation of the denervated tissue because of dispersion of melanin granules within the cell.[10,11] However, cervical sympathectomy in man, followed by development of the Horner syndrome, causes no change or decrease in eye color. This phenomenon is contrary to that observed in skin. A further difference between eye and skin melanocytes is that melanomas which arise from the eye metastasize at a much slower rate than those from skin. The prognosis is better for the eye melanoma.

The retina contains dark pigment granules which have been referred to as melanin and which occur in cells arranged in palisade formation. It is not known whether these cells represent melanocytes. There have been no reports of melanomas arising from these retinal cells. Pigmentation of frogs kept in the dark is increased in the skin but decreased in the retina. When these animals are allowed to remain in the light their skin lightens while the retina darkens. Thus the dispersion of melanin granules in skin melanocytes proceeds oppositely from that in the retinal pigment cells.

The melanocytes of the leptomeninges tend to be bipolar.[12] At times large nevi on the face have been associated with excessive numbers of melanocytes in the leptomeninges on the involved side.[13] Melanomas arise less commonly from these melanocytes than from those of skin or eyes. The metastatic tendency is difficult to evaluate because the patient usually dies from destruction of vital centers due to local enlargement of the tumor.

It would be interesting to transplant melanocytes from eyes or leptomeninges into skin in order to observe their development and learn whether they assume the form of skin melanocytes.

Once melanin is formed in the melanocyte, it is eliminated usually through the skin surface by being passed through the epidermis and shed with the stratum corneum. Melanin also may be absorbed by the lymphatics. In normal skin, in which melanin is constantly being formed and eliminated, depigmentation may be produced by local application of monobenzylether of hydroquinone for a minimum time of three weeks. This suggests that once melanin formation is inhibited, three weeks are required for elimination of the melanin already present in the skin. However, in some lesions, such as café au lait spots or postsunburn freckles, melanin granules may be permanently dispersed and firmly fixed within the cell.

2. Enzymic Factors in Melanin Formation. Melanin is formed by oxidation of the amino acid tyrosine in the presence of the enzyme tyrosinase. Tyrosinase is a copper enzyme complex located in mitochondrial elements in the cytoplasm of melanocytes. Mammalian tyrosinase is a more specific enzyme than that derived from plant or insect sources. The mammalian enzyme catalyzes

the oxidation of tyrosine and dopa more rapidly than other substrates, whereas the enzyme from non-mammalian sources is usually more effective on substrates other than tyrosine or dopa. Tyrosinase is a member of a group of enzymes, sometimes referred to as the phenolase complex, exists in some marine animals, with its pigment granules either clustered in compact masses or dispersed into minute particles.

The influence of hormonal activity on melanin granules will be considered further on. Details of the chemical steps were presented elsewhere.[15,16]

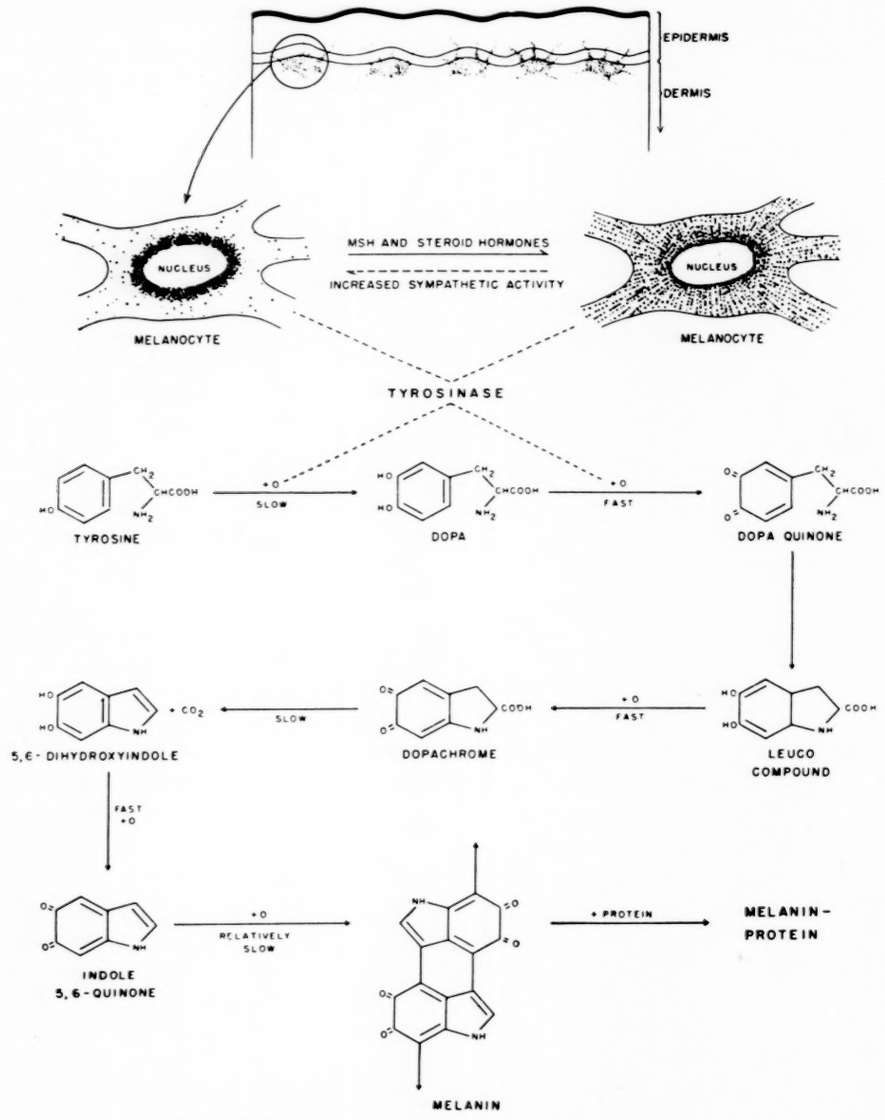


FIG. 1. Enzymic oxidation of tyrosine to melanin.

which first catalyze oxidation of monophenols to diphenols and then dehydrogenation of the diphenols to orthoquinones.[14,15] Orthoquinones are then oxidized and polymerized to a dark pigment.

On the basis of *in vitro* studies it has been possible to elucidate the conversion of tyrosine to melanin according to the steps shown in Figure 1. Here also is illustrated the melanocyte, as it

Recent studies have shown that many of the quinone intermediates in melanin formation, as well as the melanin polymer, are substances which readily react with some amino acids and proteins.[14,17] Consistent with this finding is the fact that melanin in tissues is always attached to protein.[18,19] The stage at which quinones become bound to protein is not known. However, it is possible that melanin in skin, hair and eyes is not

the same because it is formed in the presence of different proteins—proteins which vary according to their respective locations.

The mechanism of the tyrosine-tyrosinase and dopa-tyrosinase reactions has been the subject of great interest and experimentation because knowledge of these reactions is essential to the understanding of the process of melanin formation. The enzymic oxidation of tyrosine to melanin is perplexing for the following reasons. The first oxidation product, dopa, is a necessary catalyst for the oxidation, is more readily oxidized in the presence of tyrosinase and tends to accumulate as the reaction proceeds. One interpretation of the tyrosine-tyrosinase reaction, consistent with known facts, is schematized in Figure 2.[16] Cupric ions of tyrosinase are reduced to the cuprous form by a reversible reaction with dopa. For mammalian tissue this reaction is specific because not even dl-dopa is as effective as l-dopa. Non-specific reducing agents are relatively inactive with respect to mammalian tyrosinase, although quite active on plant tyrosinase. The cuprous tyrosinase-dopa quinone complex is now ready to react with tyrosine. A cuprous tyrosinase-tyrosine complex forms, and dopa quinone is released into the solution. Tyrosine is not required in the formation of dopa quinone but the specifically activated cuprous tyrosinase is needed for combination with tyrosine. The cuprous tyrosinase complex reacts with molecular oxygen to form dopa, but the copper remains in the reduced state. The cuprous ions are then oxidized to cupric ions by oxygen, and the enzyme is returned to its original state. The dopa formed from tyrosine then activates a second tyrosinase molecule which can react with tyrosine.

The dopa-tyrosinase reaction is somewhat simpler since the tyrosine reaction is absent.

The nitrogen of dopa quinone formed in the *in vitro* reactions undergoes ring closure to form the leukocompound, which in turn is oxidized to dopachrome. Dopachrome is decarboxylated to 5,6-dihydroxyindole which undergoes oxidation to indole, 5,6-quinone. The indole quinone is oxidized and polymerized to melanin. Both the leukocompound and 5,6-dihydroxyindole can react with dopa quinone to reform dopa and dopachrome, or indole 5,6-quinone, respectively. By this means dopa tends to accumulate as the reaction proceeds.

Melanin formation consequently depends upon the available concentration of three substances: (1) the enzyme tyrosinase, (2) the substrate tyrosine, and (3) molecular oxygen. The absence of any one of these results in decreased melanin formation. For example, in albinism melanocytes are present in the skin but melanin is not formed because of a genetic absence of tyrosinase in the cytoplasm of the pigment cells.

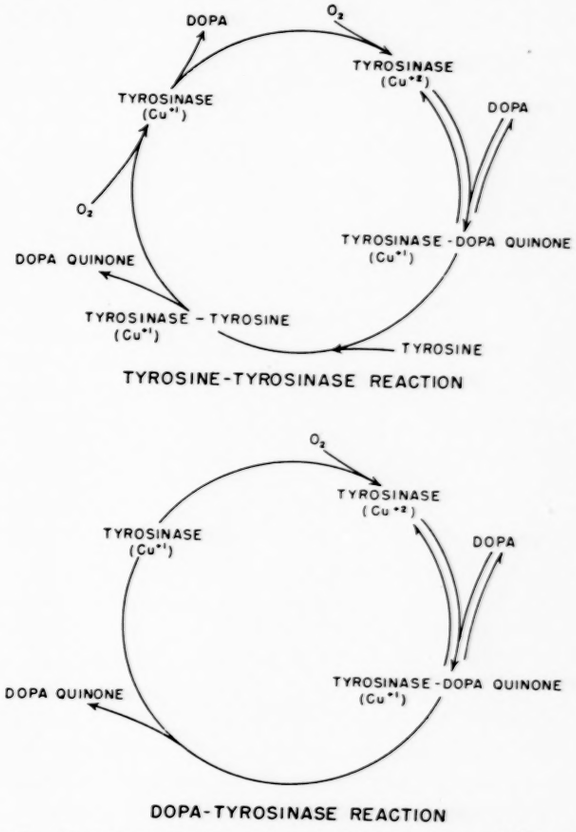


FIG. 2. Reactions of tyrosinase with tyrosine and dopa.

Enzymic control of pigmentation can be correlated with various clinical conditions.[2,15] The reaction of the three basic substances is controlled by several physiochemical factors that determine the rate of melanin formation. Those of hormonal and neurogenic nature will be discussed later. It is sufficient to say at present that temperature, the redox potential within the cell, and agents which bind and inactivate the copper ions of tyrosinase, for example, sulfhydryl groups, are probably the most significant controlling factors. Ionic strength and pH appear to be relatively unimportant.

The temperature of solutions *in vitro* is an important determinant of the reaction rate of mammalian tyrosine-tyrosinase and dopa-tyro-

sinase systems.[20] The reactions proceed relatively slowly at 25°c. but become more rapid at 37°c. Thereafter the reaction rates increase until at about 50°c. when the enzyme is quickly destroyed. Definitive proof of the relationship of temperature to pigmentation *in vivo* is not available. It is reasonable to believe that increased temperature accounts in part for hyperpigmentation of the body folds (palms, axillas, groin, and so on) and mucous membranes seen in normal persons and accentuated in patients with Addison's disease. Exposure of parts of the body to heat for long periods of time, as occurs in repeated use of hot water bottles or sitting before a fireplace or hot stove each day, results in increased pigmentation termed erythema ab igne.

The oxidation-reduction potential near the location of tyrosinase within the melanocyte probably is important in the control of tyrosinase activity because so much of the rate of melanin formation depends upon the valence state of copper and whether or not dopa quinone can be reduced back to dopa. It is possible that ionizing radiations increase melanin formation not only by oxidizing sulfhydryl groups but also by producing a redox potential more favorable to the action of tyrosinase.

In vitro experiments show that sulfhydryl groups can combine with the copper of tyrosinase and inhibit its action.[21] Epidermal extracts contain a diffusible sulfhydryl substance which inhibits tyrosinase *in vitro*.[22] Whether or not this type of inhibition occurs *in vivo* is difficult to ascertain. Available data suggest that it does. For example, one variety of neurospora is dark in color when the organism produces less of a sulfur compound.[23] Also, in mammals, staining technics demonstrate a lack of sulfhydryl groups in the hair bulb in the vicinity of melanocytes.[24] This finding is consistent with the fact that black hair can grow out from white skin. A patient whose hair was predominantly brown, except for a few gray areas, developed increased graying of the hair after each of two courses of BAL therapy for arsenic intoxication.[25] Analyses of light and dark skin of another patient revealed more sulfhydryl groups in the light skin.[26] However, these experiments did not take into account the possibility that the melanin formed in the darker skin may have combined with the sulfhydryl groups, thereby decreasing their concentration.

It has been suggested that oxidation of sulfhydryl groups by ultraviolet light is an important factor in suntanning, that the combination of sulfhydryl groups with arsenic results in hyperpigmentation, and that the destruction of sulfhydryl groups in the skin during inflammatory processes results in postinflammatory pigmentation.[15,22,27]

3. Hormone Control of Pigmentation. An array of pigmentary phenomena in man and animals provides colorful testimony of the importance of hormones in the pigmentation of skin, hair and feathers. For example, skin darkens during pregnancy, in Addison's disease and in some cases of chronic hyperthyroidism. Skin becomes lighter in color in patients with hypopituitarism. Administration of diethylstilbestrol to a hypoovarian female resulted in hyperpigmentation of the nipples and genitalia. The skin of eunuchoid males does not become pigmented after exposure to ultraviolet light unless the patient receives treatment with androgens. Under proper conditions, local application of estrogens and androgens to human beings, guinea pigs and birds produces hyperpigmentation. Estrogens and thyroid extracts modify feather coloring of chickens. Even more spectacular than these observations are experiments showing that removal of the pituitary gland in aquatic animals, such as the frog, results in decreased coloring of the skin whereas injection of pituitary extracts results in marked hyperpigmentation. These findings give added emphasis to the role of hormones in the control of pigmentation.

A. Pituitary hormones: The intermediate lobe of the pituitary gland produces two polypeptides, the melanocyte-stimulating hormones α MSH and β MSH, which can effect increased darkening of melanocytes in man and some animals.[28] (Fig. 3.) These hormones also have been called the melanophore hormone, the melanophore dilating principle, intermedin, and so on. Alpha MSH activity in pituitary extracts is about three times that of beta MSH. Both substances have molecular weights of approximately 4,000 and contain about fifteen different amino acids.[29] As little as 10^{-10} gm. of pure α MSH darkens small pieces of isolated frog skin. This hormone is distinct from other pituitary hormones. However, purified adrenocorticotrophic fractions show small but perceptible MSH activity. The converse is not true; that is, purified MSH possesses no intrinsic adrenocorticotrophic activity. This situation is similar to that of the posterior pituitary hormones, vasopressin and

oxytocin. Vasopressin possesses some intrinsic oxytocin activity although oxytocin has no vasopressin action.

Administration of MSH to human subjects produces hyperpigmentation resembling that seen in Addison's disease.[28] Darkening of the skin is generalized, although more pronounced on the exposed areas. Pigmented nevi become darker and new nevi form. If large doses of MSH are given skin darkening may be evident within twenty-four hours. The skin returns to its previous color a few weeks after treatment is discontinued.

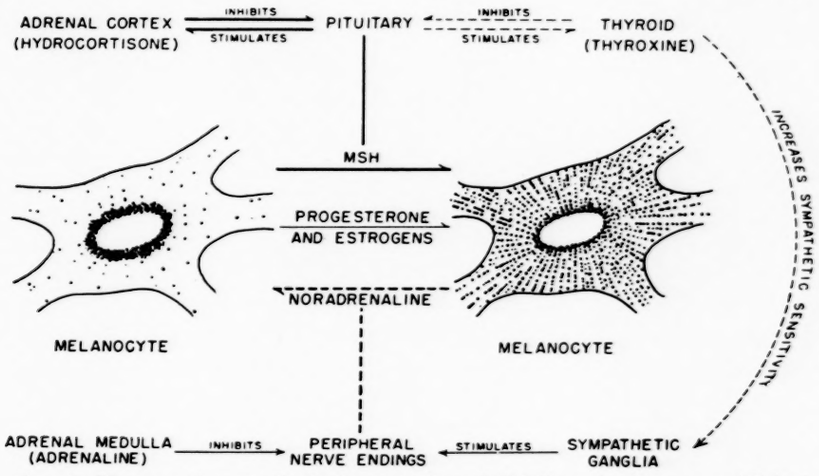


FIG. 3. Hormonal control of pigmentation. Solid lines represent established reactions; dotted lines represent possible reactions; the more prominent reactions are shown by wider lines.

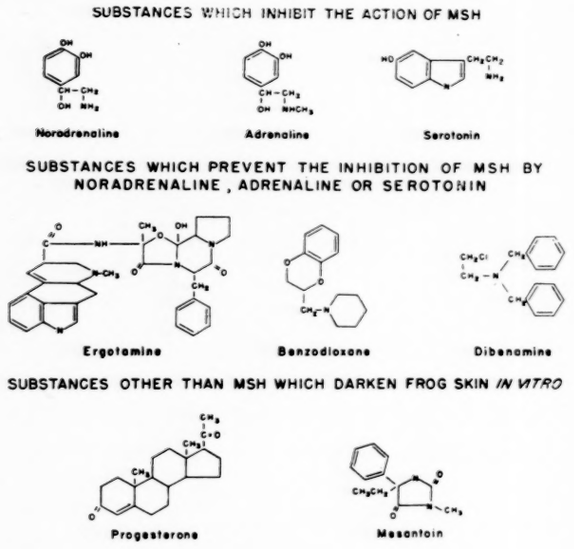
Skin reflectance measurements of white eunuchoid men and ovariectomized women before and after treatment with androgens or estrogens, respectively, showed that darkening of skin following treatment was due primarily to an increase in cutaneous blood flow.[30] Relatively little change in melanin pigmentation was observed. Variations of skin color during the menstrual cycle also were thought to be due primarily to changes in cutaneous blood flow. Some aspects of these experiments should be repeated with a view towards following more closely the changes in melanin pigmentation. Large doses of MSH produce rapid darkening of the skin in man. This effect is much more striking in more pigmented people, such as Negroes, than in fair skinned persons. Variations in skin color in a person under stress, during the menstrual cycle and in conditions of endocrine imbalance might also be due to fluctuations in melanin pigmentation. These changes are best observed in dark skin.

Blood and urine MSH can be determined quantitatively by measuring photometrically the degree of darkening of isolated frog skin produced by extracts from these fluids. Urine specimens from normal subjects contain some MSH. The excretion of this hormone is increased during pregnancy, in Addison's disease and in alopecia areata.[31,32] It was increased in the blood of a dog and in rats that had undergone bilateral adrenalectomy.[31,33] MSH was found to be absent from the urine of a hypophysectomized man.[34] MSH excretion is diminished in some patients with panhypopituitarism. The excretion is the same in white, Negro and albino persons. It is not increased in patients with malignant melanoma unless the adrenal cortices are destroyed by the tumor.

Administration of cortisone or hydrocortisone, usually given in 37.5 mg. and 20 mg., respectively, prevents darkening of the skin of bilaterally adrenalectomized human subjects or decreases darkening of skin color in patients with adrenocortical deficiency. Cortisone and hydrocortisone also reduced the levels of MSH to normal in a bilaterally adrenalectomized dog. A patient with severe alopecia areata and markedly increased levels of MSH in the urine excreted normal amounts of MSH after daily oral administration of the following steroids: 37.5 mg. cortisone, 20 mg. hydrocortisone, 5 mg. fluorohydrocortisone. These dosage values were

minimal in that smaller quantities did not produce the same effect.

Darkening of isolated frog skin by MSH can be prevented by adding small quantities of adrenaline® or noradrenaline to the solution.[35] The natural levorotatory forms are more active



than the dextrorotatory isomers. Effective but less active than adrenaline or noradrenaline is serotonin. The inhibition of MSH by these substances can be blocked by sympathomimetic drugs such as ergotamine, dibenamine,® benzodioxane and priscoline.® It is not known whether inhibition of MSH by adrenaline, noradrenaline, serotonin or a related substance has any bearing on normal human pigmentation. However, it is likely that these substances play some part.

B. Steroid hormones: In vitro, progesterone darkens frog skin.[35] Production of progesterone, as well as of MSH, is increased with progression of pregnancy; skin pigmentation follows a similar course. However, local application of progesterone to guinea pig nipples produces no change. Daily application of estrogenic substances to guinea pig nipples produces enlargement and marked darkening of the nipples. Administration of diethylstilbestrol to a hypoovarian female resulted in darkening of the nipples, linea alba and pigmented nevi.[36] The skin of patients with chronic liver disease becomes very dark, presumably because of increased circulating estrogen.[37] Administration of estrogens to a male brown leghorn fowl produces a pigmented feather pattern of the female type.[38] Testosterone has no effect on fowl pigmentation. However, locally applied testosterone induces pigmentation of the bill of the sparrow[39] and the scrotum of the ground squirrel.[40] Eunuchoid males given testosterone are enabled to acquire a good suntan.[41] From these observations it is evident that progesterone, estrogens and androgens alter skin color but the effect varies from one species to another. It is not known whether the blood level of these steroids can affect the release of MSH from the pituitary gland. As mentioned previously, cortisone and hydrocortisone influence pigmentation, not directly, but at the pituitary level by inhibiting the formation or release of MSH.

C. Thyroid hormones: Thyroxine is required for normal pigmentation of the feathers of male and female brown leghorn fowls.[38] Injection of crude thyroid extract into rainbow trout blanches the skin.[42] The active agent is not thyroxine, diiodotyrosine or an inorganic iodide compound. There is a clinical impression that patients with hyperthyroidism tend to have vitiligo, although it is uncommon for patients with vitiligo to have hyperthyroidism. One patient with hyperthyroidism and vitiligo experienced complete repigmentation following thyroidectomy.[43]

From these observations it is apparent that the thyroid gland plays a part in pigmentation. However, its exact status is not established. Little is known concerning the relationship of the thyroid gland to the output of MSH by the pituitary gland.

D. Other hormones: It has been claimed that the pars tuberalis contains a substance which exerts an opposite effect from that of MSH on the toad and eel.[44,45]

Two drugs, mesantoin and chloroquin, recently were shown to affect pigmentation. Although their mode of action is not known to be hormonal, they will be mentioned briefly. Prolonged administration of mesantoin, an anticonvulsant, has been associated with hyperpigmentation resembling that of Addison's disease.[46] This drug has an MSH-like action on isolated frog skin.[35] It is possible that it can exert an MSH-like action in man also. Chloroquin has lightened the hair color of some children about four weeks after its administration for treatment of lupus erythematosus.[47,48] Whether these drugs produce a change in pigmentation through a hormonal, neurogenic or enzymic process has not been established.

E. Mechanism of hormone action: A most important problem is determining the action of

hormones on melanocytes. Through what mechanism do MSH and progesterone darken melanocytes, and how do substances like adrenaline, noradrenaline and serotonin inhibit MSH activity? The effect of MSH on frog melanocytes is rapidly reversible. Under proper conditions *in vitro* the cells may darken in about fifteen minutes and lighten again in a similar period of time. Darkening is brought about by dispersion of the conglomerate masses of melanin pigment granules. Relatively little change occurs in the over-all size and shape of the melanocyte during this process.[49] Oxygen is required for optimum darkening but not for the lightening process. MSH does not darken melanocytes in a stream of hydrogen. Agents that block sulfhydryl groups inhibit the action of MSH, although in themselves they can darken melanocytes. Melanocytes placed in solutions of low pH or ionic strength deepen in color. The physical change inside the cell induced by MSH is closely related to the biochemical integrity of the melanocyte. This phenomenon is similar to that of muscular contraction, a physical change which nonetheless is closely related to the biochemical reactions occurring in the muscle fiber.

The variations in the melanocyte which take place shortly after addition of MSH are probably different from those observed after the cell has been kept in a darkened state for long periods. In the latter case there is probably an increase in new melanin formation. While small amounts of MSH effect a reversible darkening of frog melanocytes *in vivo* or *in vitro*, large amounts produce permanent darkening.

4. Neurogenic Control of Pigmentation. Melanocytes are derived from the neural crest and resemble nerve cells in several respects. They are dendritic in shape, produce dopa which is similar in chemical structure to noradrenaline produced by some nerve tissue, and give rise to neoplasms which do not respond to x-ray therapy any more favorably than do most nerve cell tumors. It is therefore not unexpected that melanocytes should be subject to some type of neurogenic control.

In fish, sectioning the sympathetic nerve to a fin results in darkening of that fin. As the nerve regenerates, the fin returns to its normal color. On the other hand, faradic stimulation of the intact nerve causes blanching of the fin.

Examples of neurogenic factors in human pigmentation are numerous. In 90 per cent of patients with neurofibromatosis pigmented macules or café au lait spots are present. The exact etiology of these lesions is not known but it is interesting that they appear in persons with nerve lesions.

There is some evidence to support the view that vitiligo is caused by increased activity of the sympathetic nervous system at the peripheral nerve endings. A patient with vitiligo and transverse myelitis had no depigmentation below the level of paralysis, whereas usually in vitiligo depigmentation is observed on the lower portions of the body. Another patient developed vitiligo several years after having had poliomyelitis. There was less depigmentation on the leg having nerve damage.

Opposed to the observations in vitiligo is the finding that following cervical sympathectomy and production of the Horner syndrome the iris of the involved eye either remains unchanged or becomes lighter in color. As mentioned earlier, the melanocytes of the eye may respond to different neurogenic control than do those in the skin.

The view is held among ophthalmologists that melanomas of the eye arise primarily from nerve cells of the sheath of Schwann where the nerve fibers traverse the uveal tract.

In addition to these clinical observations are the previously discussed *in vitro* findings that two hormones, adrenaline and noradrenaline, both produced by nerve tissue, can inhibit MSH action and cause blanching of frog melanocytes.

At the present time a moderate amount of information is available concerning the cytology of melanocytes and the control of pigmentation by enzymic and hormonal factors. It is hoped that our knowledge of neurogenic control will be similarly expanded.

NORMAL PIGMENTATION

In normal persons the color of skin, eyes and hair may vary from near white to black. These differences in pigmentation are not due to variations in the number of melanocytes but rather to the pigment producing capacity of the melanocytes in a given subject. The amount of pigment in a particular melanocyte is determined by the balance of enzymic, hormonal and neurogenic factors. The albino, white man and Negro have approximately the same number of melanocytes in any particular location. Equal quantities of urinary MSH are excreted. But in the albino there is a genetic absence of

tyrosinase so that melanin cannot be formed. It is possible that the darker skin coloring of some races may be explained in one or more of the following ways: (1) The total amount of tyrosinase available for melanin formation may be increased. (2) The normal inhibitors of tyrosinase may be decreased. (3) An oxidation-reduction potential in the melanocyte may be more favorable for tyrosinase action.

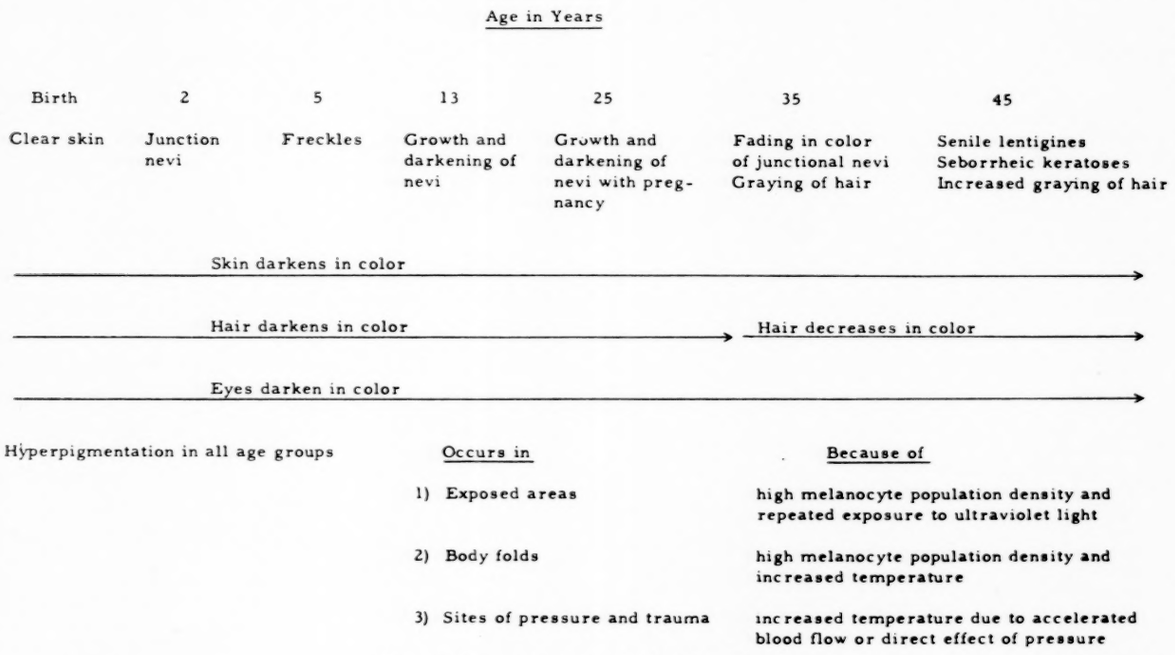


FIG. 4. Normal pigmentation life chart.

At birth the skin is usually free from pigmentary lesions. Only 2.7 per cent of white infants, but 15.6 per cent of Negro infants, were reported to have pigmented lesions at birth.[50] Sixty per cent of Negro infants and 0.5 per cent of white infants have sacral or mongolian spots. These blue-colored areas represent diffuse collections of pigmented melanocytes in the dermis. Usually they cease to be visible after a few years.

With growth and aging, the skin, eyes and hair become darker. (Fig. 4.) This increased darkening is especially notable between birth and puberty in persons of fair or medium dark coloring. It is common for a child with almost snow-white hair in infancy to develop dark brown hair by the time puberty is reached. Hair frequently darkens following a severe illness. Late in life hair becomes gray. The infant who is blue eyed at birth may become brown eyed at a few months of age. Afterwards the eyes continue to darken, and the rate of darkening is greater in the female. Negroes are often light in color at birth but become much darker within two weeks. Their eyes undergo rapid change from light brown to dark brown or black.

At about two years of age pinpoint-sized, flat, pigmented spots appear, usually on the upper portions of the body. They frequently follow stress reactions, such as a severe cold or one of the infectious diseases of childhood. These minute lesions are junctional nevi which develop as a result of increased melanocyte activity at the epidermal-dermal junction. In very light complexioned children or in albinos the nevi are flesh colored. They usually increase in size and color with increasing growth and development of the child and with the advent of new illnesses. It is possible that MSH released from the pituitary gland during periods of stress is responsible for the nevi.

Although nevi will be discussed in detail later, some aspects will be considered now. According to textbook connotation, there are an average of twenty nevi per person, although they may vary from one to a hundred. However, no data have been given to support this impression. Nevi counts should be done in both sexes, at different ages and for different types of skin coloring. An early nevus may follow one of several courses. It may remain unchanged in size, it may increase or regress. Usually all these changes occur but at

different periods; that is, after the initial appearance of the nevus, it may remain stationary until a new illness develops or until puberty is reached. It then darkens and grows. However, later, at about the age of thirty, the nevus may show decreased melanocyte activity and regress. At the time the nevus enlarges it may develop in other ways as well. Although it may become merely a larger junctional nevus, a compound nevus results if some melanocytes move into the dermis while others remain at the basal layer. A dermal nevus forms if all the melanocytes are limited to the dermis proper.

At five to seven years of age some persons develop freckles on areas exposed to sunlight. Freckles are prominent from their onset until about the age of twenty when they become less apparent.

During puberty nevi darken and grow and new ones appear. A similar course is noted in pregnancy.

During the thirties graying of hair may become evident. In the forties new nevi cease to appear but senile lentigines, popularly known as liver spots, and seborrheic keratoses may form. Senile lentigines will be discussed later. Seborrheic keratoses are hyperkeratotic, greasy-surfaced lesions which are often very dark. Their color is in part due to melanin.

In normal persons pigmentation is not uniform over the entire body. Hyperpigmentation occurs on all exposed areas, such as the face, neck and hands, in the body folds, such as the axillas, groin and palms, and at the sites of pressure and trauma, such as the location of cuts, burns or the wrist band area. A darkening of these regions may result from one or more of the following conditions: (1) high melanocyte population density, (2) repeated exposure to ultraviolet light, or (3) increased temperature due to accelerated blood flow or direct effect of pressure.

Those areas that are normally hyperpigmented are labile insofar as color is concerned. In diseases with a tendency towards hyperpigmentation, Addison's disease for example, the sites of physiologic hyperpigmentation become darker. In vitiligo the same areas become lighter. These observations are so constant that from them a law of skin pigmentation can be formulated: Normal areas of hyperpigmentation are predisposed to change either in the direction of more hyperpigmentation or depigmentation.

VARIATIONS IN MELANIN PIGMENTATION

A classification of variations in skin pigmentation is outlined in Table 1. The list is made up of entities which either are common or else illustrate a basic process pertaining to pigmentation. It is worth while pointing out the reasons for using this type of classification. In the past, efforts were made to divide pigment abnormalities into two main groups based upon either local and systemic factors or those of external and internal origin. Such schemes are confusing because of much overlapping in the two groups. In Table 1, nine different etiologic groups are divided according to hyperpigmentation or hypopigmentation. Here, too, overlapping of the etiologic groups occurs; for example, although the ability to freckle is genetically transmitted, the physical factor of ultraviolet light is a necessity for their development. The tendency to form junctional nevi may be genetic in part but also is intimately related to hormonal factors. Vitiligo may be placed in either the genetic or neurogenic groups. Other examples of overlapping will be apparent. In spite of these limitations the classification is easy to understand and simple to use. Each entity will be discussed briefly.

1. Genetic Factors. The variations in pigmentation from one person or race to another were discussed in the section on normal pigmentation.

Freckles or ephelides (Fig. 5A) are associated with a single dominant gene which is linked with that for red hair. Both genes are associated with the same chromosome. A high correlation exists between freckles and red hair but a low one between freckles and eye color. Freckles are round or irregularly shaped flat spots which are light brown in color. They vary in size and occur chiefly on exposed areas such as the face, neck, upper back, shoulders and backs of hands. The lesions appear initially at about five years of age and develop after exposure to sunlight. Freckles darken during the summer and lighten in winter. Their color fades in adult life. Microscopically a freckle shows only hyperpigmentation of melanocytes at the epidermal-dermal border.

Pigmented nevi can be divided into four groups depending upon the site of melanocyte proliferation: Junctional nevi or lentigines (Fig. 5B) arise from proliferation of melanocytes at the epidermal-dermal junction. They are usually brown to black hairless macules. They

are by far the commonest type of nevus and can be produced by injections of MSH. Compound nevi are composed of melanocytes at the epidermal-dermal junction and in the dermis. They vary from colorless to black, may be flat or raised and may or may not contain hair. Their rate of occurrence is second to junctional nevi. Dermal nevi consist of melanocytes grouped in the dermis. Clinically they resemble compound nevi but occur less frequently. Blue nevi are a form of dermal nevi which usually occur in the lower two-thirds of the dermis. The color varies from blue to black depending upon the quantity and location of melanin in the dermis. They are seen most frequently in persons belonging to the Oriental races.

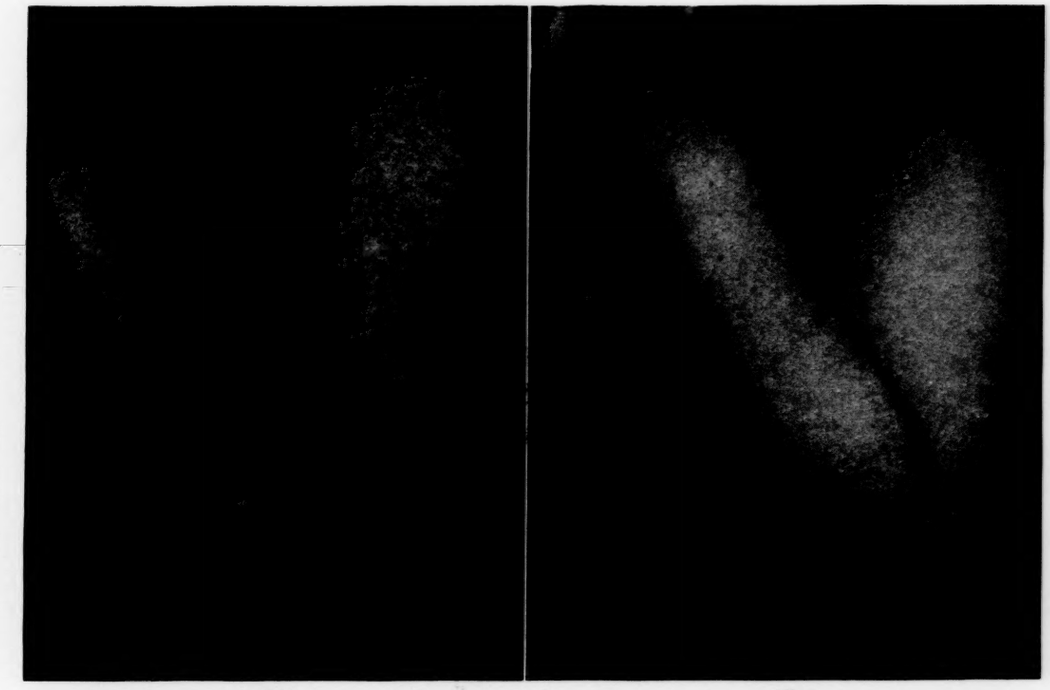
Most nevi appear after birth, but some large pigmented ones are present at birth. (Figs. 6A and B.) They probably are a result of abnormal migration of melanocytes from the neural crest to the skin. The factors controlling this migration are not known. These nevi may be only a few millimeters in size or large enough to cover most of the body. The elements of junction, compound and dermal nevi may all occur in one lesion. Occasionally malignant change has been reported. Some women who have large nevi believe they darken at menstruation.

The development of nevi with age was discussed earlier. Most nevi are usually new growths, and there is no evidence that their

TABLE 1

VARIATIONS IN MELANIN PIGMENTATION

Etiologic Factors	Hyperpigmentation	Hypopigmentation
Genetic	Racial factors Freckles (ephelides) Pigmented nevi Senile lentigines	Albinism (partial or total) Premature graying of hair
Physical	Ionizing radiations Heat	Severe thermal burns Severe trauma
Chemical	Heavy metal intoxication Photosensitization (psoralens, tar)	Hydroquinone derivatives Chemical burns
Endocrine	Addison's disease ACTH therapy Hyperthyroidism Acromegaly Pregnancy Estrogen or androgen therapy Chronic hepatic insufficiency	Addison's disease Panhypopituitarism Hyperthyroidism
Neurogenic	Café au lait spot Lines of demarcation	Vitiligo Alopecia areata
Nutritional	Chronic malnutrition Niacin deficiency (pellagra)	Pantothenic acid deficiency Para-aminobenzoic acid deficiency
Infectious and inflammatory	Chronic systemic infections (e.g., TBC) Chronic dermatoses	Leprosy Pinta
Neoplastic	Chronic illness with neoplasm Acanthosis nigricans Melanoma	.....
Unclassified	Scleroderma Hemochromatosis Skin graft Polyostotic fibrous dysplasia Intestinal polyposis	Scleroderma Skin graft



5A 5B

FIG. 5. A, freckles; lighten in winter and darken in summer B, junction nevi or lentigines; not present at birth; very common.

origin is from congenital misplaced cells which hitherto were unrecognized. It is possible that because of local anatomic variations such as blood supply MSH, produced by a stress response, stimulates the formation of new nevi. However, blue nevi may represent collections of melanocytes which in their embryonic development failed to reach the epidermal-dermal junction.

While the tendency to form nevi is partially under genetic control, MSH is an important contributing factor.

Senile lentigines are yellow to brown, vary in size and may be as large as a centimeter in diameter. They usually occur in adults in areas repeatedly exposed to sunlight, such as the hands and face. The layman refers to senile lentigines as "liver spots" because their color resembles that of fresh liver. Microscopically they are similar to lentigines or junctional nevi. However, they occur in people with a genetic tendency to their formation after the skin has been exposed to sunlight for many years.

Albinism in the experimental animal is transmitted as a non-sex linked, simple Mendelian recessive factor. Albinism is present from birth. It may be divided into complete, incomplete and partial types. Pigment does not form because of genetic absence of tyrosinase in the melanocyte. (Fig. 6C and 6D.)

In cases of premature graying of hair, as in vitiligo, the age of onset tends to follow a genetic pattern. However, additional factors, particularly neurogenic, are probably involved. The pigment law, if carried to the extreme, might permit the conclusion that formation of gray hair in normal persons is a vitiliginous process, for hair, being highly pigmented, would be likely to undergo early depigmentation.

2. Physical Factors. Ionizing radiations, such as ultraviolet light, alpha rays and x-rays, stimulate formation of new melanin and also darkening of pre-existing melanin.[15] As mentioned earlier, oxidation of sulfhydryl groups by ionizing radiations might make tyrosinase more available for melanin formation. Also one or more of the following factors may play a role: (1) The radiations may promote conversion of tyrosine to dopa so that the latter then can catalyze the tyrosine-tyrosinase reaction. (2) The oxidation-reduction potential in the melanocyte may undergo change so that tyrosinase activity is increased. (3) In the case of sunlight, temperature may be increased, allowing for acceleration in the rate of melanin formation. In addition to these three factors, melanin already

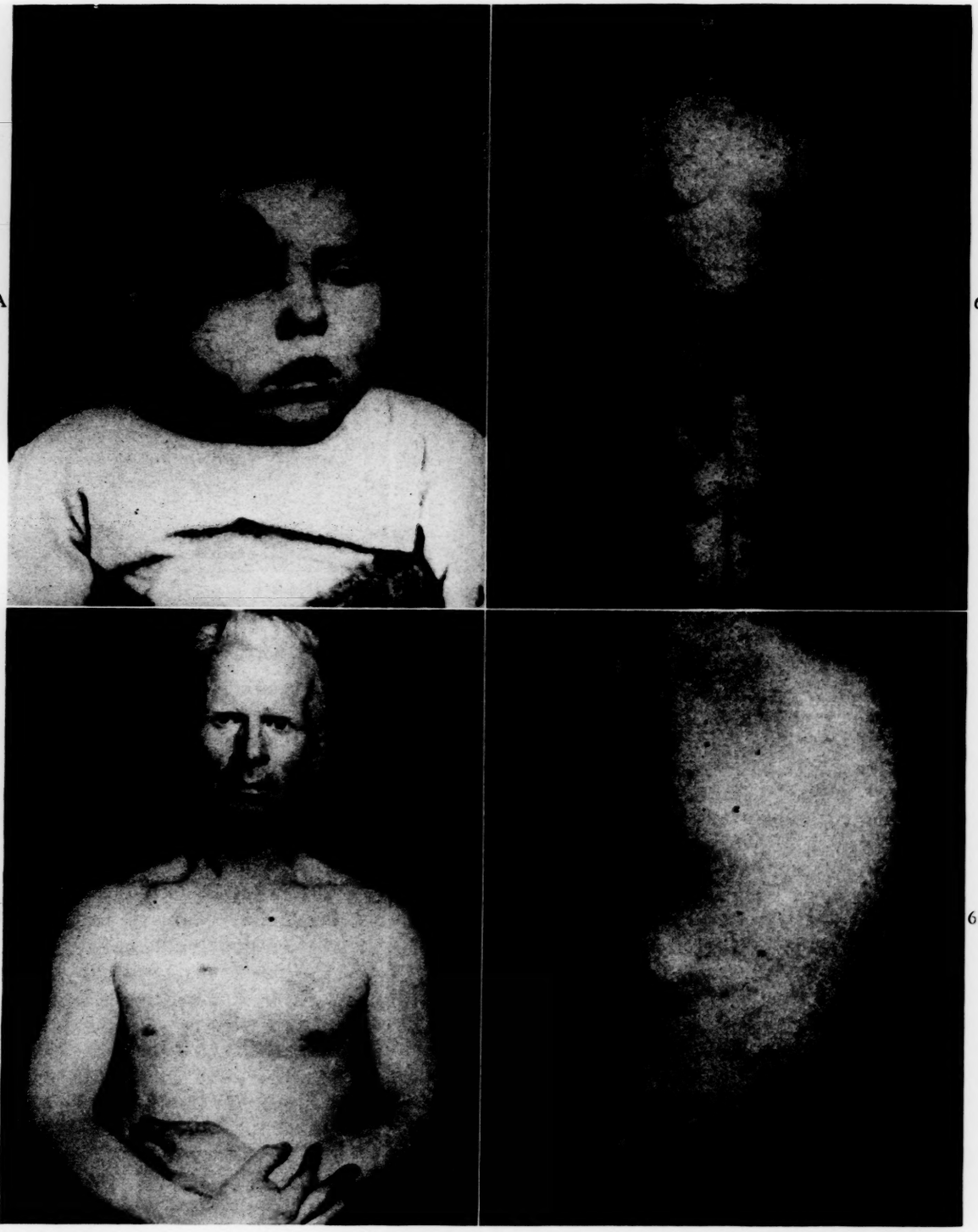


FIG. 6. A, large nevus on face present since birth; relatively rare. B, large bathing trunk nevus present since birth; relatively rare. C, complete albinism. D, partial albinism in a seven year old boy; hypopigmentation present since birth.

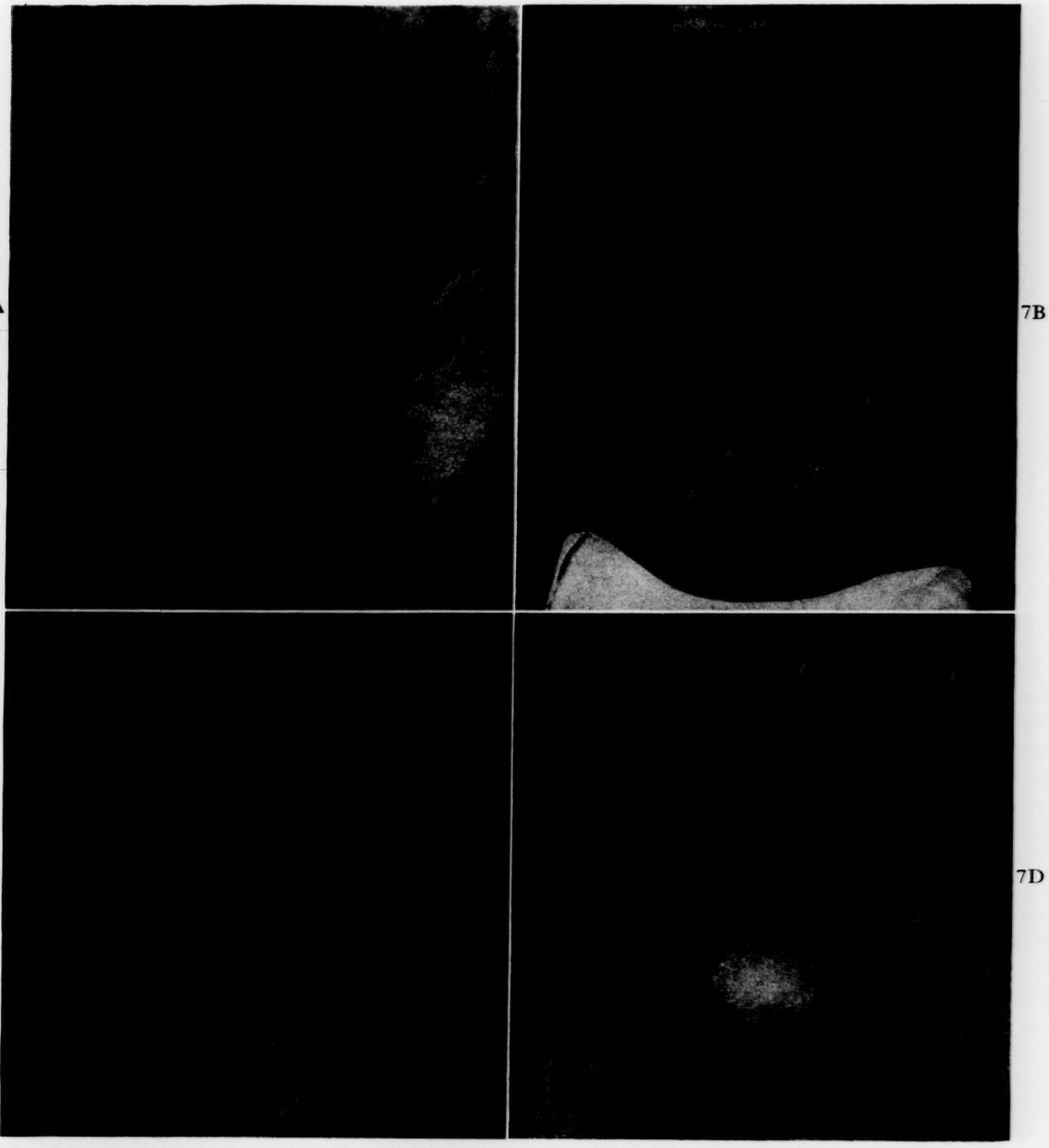


FIG. 7. A, erythema ab igne of thighs; reticulated hyperpigmentation from prolonged use of heating pad. B, hyperpigmentation following arsenic intoxication; note "raindrop" appearance of thoracic pigment. C, marked hyperpigmentation following application of 8-methoxypsoralen and subsequent exposure to sunlight. D, localized depigmentation of Negro's back after four weeks' continuous application of an ointment containing 20 per cent monobenzylether of hydroquinone.

present may become darker because of oxidation to a darker form.

In most instances a suntan or other type of radiation-induced hyperpigmentation fades a few days or weeks after the provocative stimulus, and the skin returns to its previous shade. However, this sequence is not invariable. Sometimes a severe sunburn is followed by large freckles which remain permanent. Intensive exposure to roentgen rays may produce lasting hyperpigmentation. Why this hyperpigmentation should persist is not known. Perhaps the pigment formed under this profound stimulus is permanently dispersed in the melanocyte, much in

the manner of the irreversible darkening produced in frog melanocytes by administration of huge amounts of MSH.

Years ago reticulated hyperpigmentation, or erythema ab igne, was common on the legs of people who regularly exposed themselves to the heat of a fireplace or stove. (Fig. 7A.) Today this type of pigmentation is less common but it still occurs in persons who use hot water bottles for long periods of time and in workers who are frequently in proximity to hot furnaces. Hyperpigmentation probably results from a direct increase in temperature, as well as an indirect one through heightened vascularity, which accelerates the tyrosine-tyrosinase reaction.

Thermal burns or trauma to the skin severe enough to destroy melanocytes results in depigmentation. Like most nerve cells, melanocytes regenerate slowly.

3. Chemical Factors. Administration of arsenic, silver or bismuth compounds, may produce hyperpigmentation. Arsenic hyperpigmentation characteristically assumes a "raindrop" pattern on the exposed areas and trunk. (Fig. 7B.) Small, relatively pale spots are scattered throughout the areas of hyperpigmentation. Arsenic hyperpigmentation may be difficult to distinguish from that seen in Addison's disease. Arsenic keratoses may occur, especially on the palms and soles.

Patients with silver (argyria) or bismuth intoxication develop slate gray or blue hyperpigmentation on the exposed areas which imparts a cyanotic appearance. Although the increased pigmentation is seen only on areas exposed to sunlight, the metal also is deposited in the skin of the covered regions.

The hyperpigmentation from arsenic may be due to inactivation of sulfhydryl groups, making copper more available for tyrosinase action. Most of the hyperpigmentation from silver and bismuth is not due to melanin but represents deposits of the metallic metal in the skin, especially in the sweat glands.

In photosensitization, several substances, particularly the psoralen derivatives present in many essential oils, increase pigmentation when applied to the skin or taken orally prior to ultraviolet light exposure. (Fig. 7C.) The mechanism of this process is unknown. 8-Methoxypsoralen can be used to treat some patients with early and limited vitiligo.[8]

In the case of hydroquinone derivatives, depigmentation occurs in some persons following application of monobenzylether of hydroquinone. (Fig. 7D.) Evidence is present that the tyrosine-tyrosinase reaction is inhibited by hydroquinone formed from the monobenzylether of hydroquinone.[51]

Chemical burns may cause depigmentation resulting from destruction of melanocytes.

4. Endocrine Factors. Patients with adrenocortical insufficiency (Addison's disease) frequently show hyperpigmentation of the exposed areas, body folds, sites of pressure and trauma, and of the mucous membranes. (Fig. 8A and 8B.) Nevi darken and new nevi form. Occasionally these patients develop vitiligo with depigmentation in these areas, but with marked hyperpigmentation of the rest of the skin.

Increased release of MSH from the pituitary gland occurs following decreased adrenocortical function. MSH markedly accentuates pigmentation in those areas where hyperpigmentation normally occurs and may induce formation of new nevi.

The depigmentation in some patients with adrenal insufficiency may be explained by assuming that extensive destruction of the adrenal glands evokes a compensatory increase in sympathetic activity resulting in vitiligo. In these patients the hyperpigmenting and depigmenting processes proceed simultaneously.

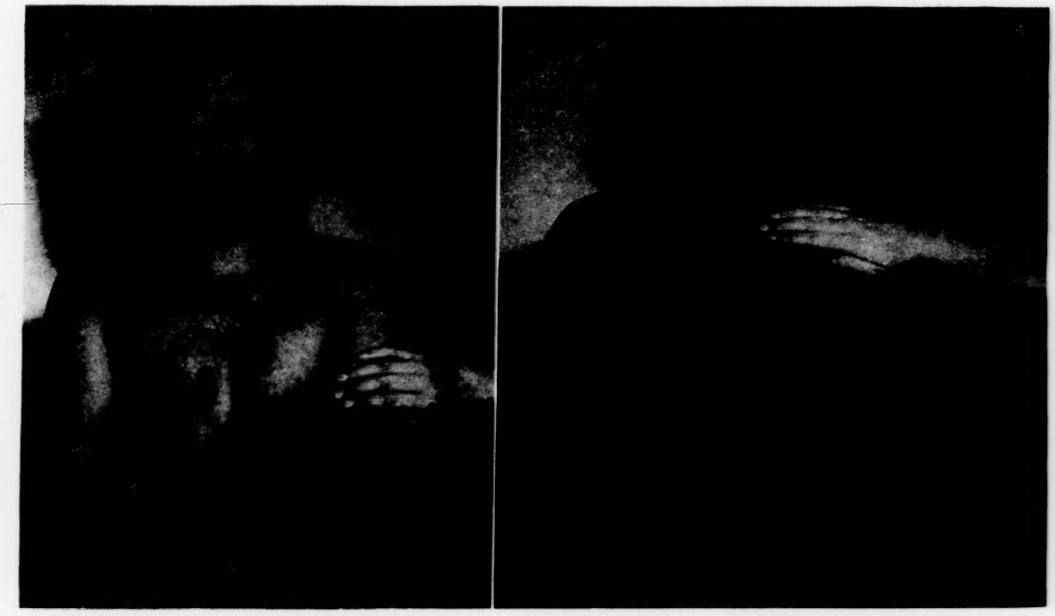
Prolonged administration of ACTH may produce hyperpigmentation because of MSH present as a contaminant in the ACTH preparation.

It is frequently remarked that patients with early hyperthyroidism tend to have vitiligo but no statistical study on this point apparently has been made. Hyperpigmentation sometimes occurs in severe, chronic hyperthyroidism, possibly because of increased release of MSH from the pituitary gland.

Hyperpigmentation when present in acromegaly may be due to MSH.

Hyperpigmentation (melasma*) develops over the face, usually in a blotchy fashion, constituting the "mask" of pregnancy. The nipples, genitalia and linea alba darken. Nevi may deepen in color and increase in size. Several hormones which affect melanocytes increase in the blood and urine during pregnancy. The

* In this paper the term melasma refers to the hyperpigmentation occurring usually on the exposed areas, body folds or sites of trauma associated with increased urinary excretion of MSH.[52] The brown discoloration which occurs during pregnancy is due to melasma rather than to any green pigment. It is more correctly designated melasma then chloasma.



8A 8B

FIG. 8. A, anterior view of twenty-seven year old man with Addison's disease of seven years' duration; compare color with hand of normal subject selected by patient as representing his complexion prior to illness. B, back of patient shown in Figure 8 A; note hyperpigmentation of palmar creases and scars on back.

levels of MSH, progesterone and estrogens rise with progression of pregnancy. Within five days after delivery MSH levels return to within normal limits. It is possible that all of these factors contribute to melanocyte darkening. In most patients pigmentation fades a few months after delivery; however, pigmentation sometimes is permanent.

In white persons with estrogenic or androgenic deficiency the skin has a pallor due largely to decreased cutaneous blood flow. Administration of the deficient hormones corrects this situation. The hormones also may affect melanin pigmentation, particularly in the darker subjects.

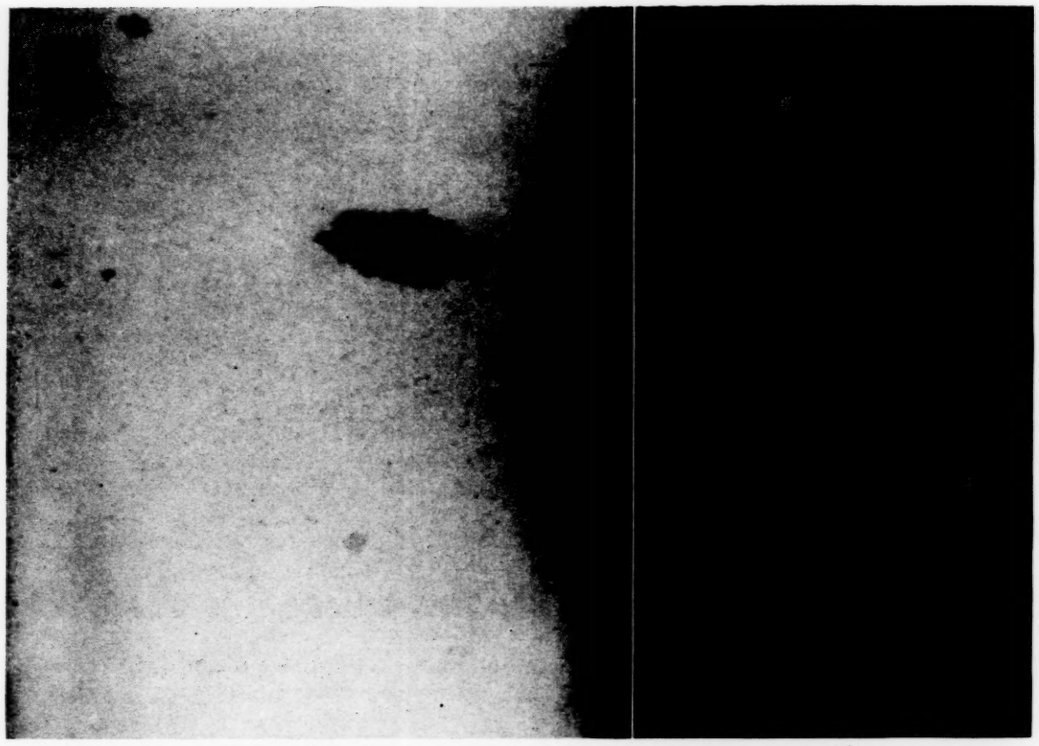
Some patients with chronic hepatic insufficiency become very dark. It has been suggested that increased circulating estrogens are responsible for this hyperpigmentation.[37]

In panhypopituitarism the skin is light because circulating MSH is decreased as a result of reduced pituitary function.

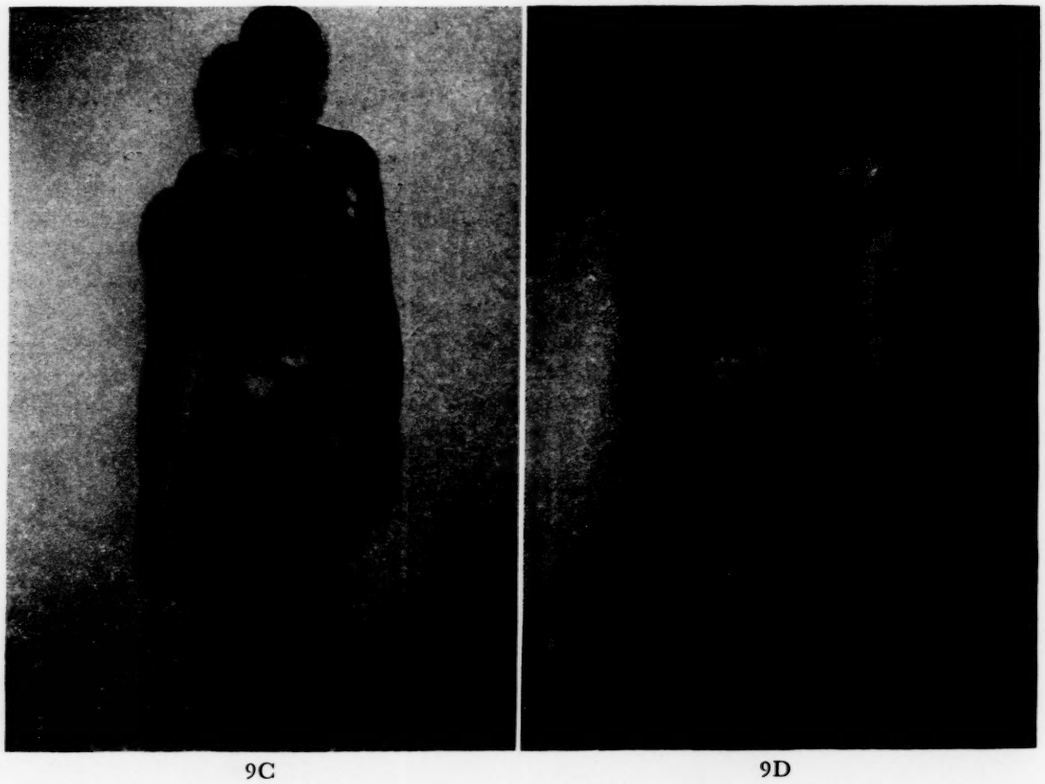
5. Neurogenic Factors. Café au lait spots (Fig. 9A) are hyperpigmented macules of variable size and shape which usually appear after birth. Approximately 10 per cent of normal persons and 90 per cent of patients with neurofibromatosis have café au lait spots.[53,54] However, only 0.2 per cent of normal persons have three or more whereas about 75 per cent of those with neurofibromatosis have this number. Microscopically café au lait spots show hyperpigmentation of the basal layer and are indistinguishable from the ordinary freckle. These lesions are grouped with factors under neurogenic control because patients with neurofibromatosis have nerve lesions and neural control of melanocyte function may be affected.

In people with more pigmented skin, such as the Japanese, the arms and chest of some individuals show sharply divided areas of pigmentation.[55,56] These lines of demarcation are fairly common in Negroes. (Fig. 9B.) Along the anterior aspect of the arm a sharp border may separate a lateral dark portion from a medial lighter area. It has been suggested that this sharp division of color depends upon neurogenic factors.

In vitiligo hypopigmentation occurs, usually in one or more of the following areas: hands, arms, face, neck, axillas and inguinal regions.[57] (Fig. 9C and 9D.) Approximately 1 per cent of the total population of this country has vitiligo. In 50 per cent of the cases hypopigmentation develops before the age of twenty. Repigmentation to some degree, although not complete, occurs in 50 per cent of patients with vitiligo at some time in the course of their illness, usually in the summer following exposure to sunlight. In



9A 9B



9C 9D

FIG. 9. A, café au lait spots. B, line of demarcation on Negro's arm; common. C, vitiligo; note involvement of common sites, face, arms, umbilicus and genitalia. D, posterior view of patient shown in Figure 9 C.

50 per cent of the cases relatives are found to have vitiligo. The inherited tendency toward development of vitiligo is expressed as a dominant factor. The hypopigmentation usually becomes more extensive following severe stress such as an acute illness or operation. Although the etiology of vitiligo has not been determined, the following points suggest that hypopigmentation may result from increased activity of the sympathetic nervous system at the peripheral nerve endings near the melanocytes: (1) L-noradrenaline tested on isolated frog skin was found to be a specific inhibitor of MSH. Frog melanocytes became light in color upon addition of noradrenaline.[35] (2) In some fish sectioning of a fin nerve results in darkening of skin distal to the section. Upon regrowth of the nerve the skin becomes light again. Faradic stimulation of the intact nerve produces a decrease in color. A patient with transverse myelitis of thirteen years duration developed vitiligo four years ago and no depigmentation has occurred below the level of paralysis.[57] (3) Vitiligo often occurs in segments corresponding to nerve distribution.[57–59] (4) Under resting conditions, more sweat occurs in areas of vitiligo than on adjacent pigmented skin.[57] (5) A report on the use of the capillary microscope *in vivo* indicates that blood vessels are constricted in patches of vitiligo.[60]

If a patient with vitiligo becomes jaundiced or develops yellow skin from ingestion of atabrine only the non-vitiliginous areas become yellow. The pigmentation due to bile or atabrine is not seen in the areas of melanin hypopigmentation.[88,89] Studies have not been made on the affinity of melanin or melanocytes for these other pigments.

Patients with diffuse patches of baldness (alopecia areata) and increased emotional tension frequently exhibit gray hair and vitiligo. It is possible that hypopigmentation of hair and skin is due to increased activity of the sympathetic nervous system.

6. Nutritional Factors. A few weeks on a starvation diet may produce melasma of the face.[15] If starvation is continued the hyperpigmentation may become generalized. It is possible but not proved that increased pituitary activity increases the release of MSH so that hyperpigmentation results.

In pellagra, hyperpigmentation of the exposed areas is common following subsidence of the acute dermatitis. The darkening represents the dual processes of photosensitization and post-inflammatory pigment deposition. Reduction in sulfhydryl groups following the acute reaction may be responsible for the hyperpigmentation.

Pantothenic and paraaminobenzoic acids are known to be required for normal pigmentation of the hair of some animals but not that of man. Administration of large doses of paraaminobenzoic acid to man produces repigmentation of gray hair in some subjects.[61]

7. Infectious and Inflammatory Factors. Chronic infections or almost any severe illness of long duration may be associated with development of melasma. As in other instances of melasma, it may be of endocrine etiology.

Hyperpigmentation accompanies prolonged rubbing and scratching of the skin indulged in by patients with chronic dermatoses such as severe atopic dermatitis or postinflammatory lesions. (Fig. 10A.) Increased temperature and destruction of sulfhydryl groups may increase melanin formation.

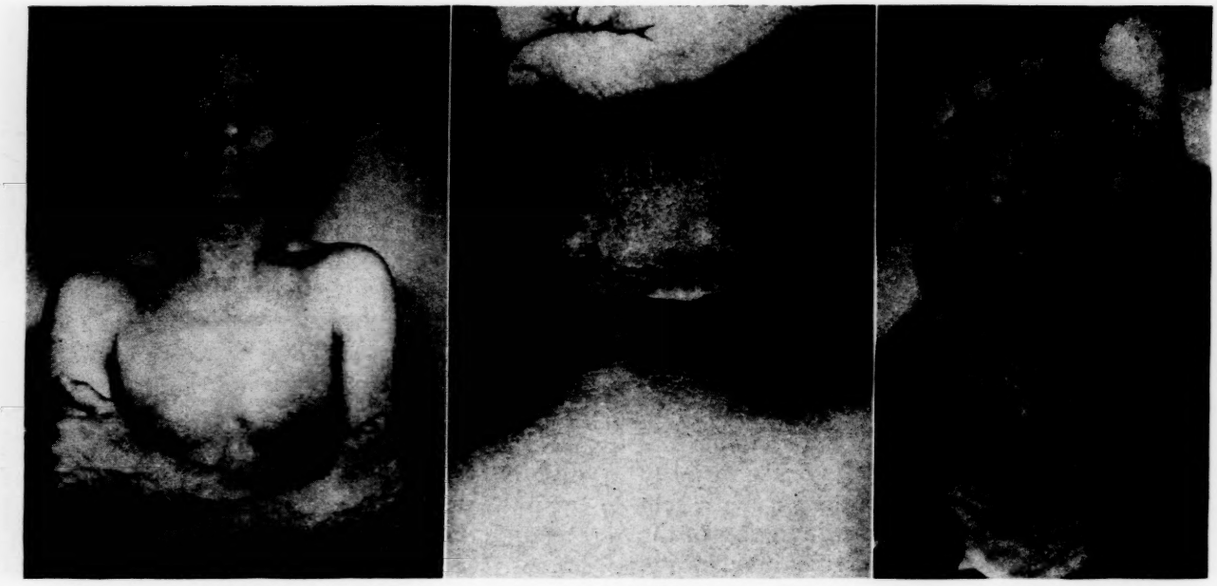
Hypopigmented macules are common in leprosy, especially in the tuberculoid type.[62] In such cases skin lesions are co-extensive with nerve involvement. The cause of hypopigmentation is not known; it may be neurogenic.

Hyperpigmentation is seen early in the course of pinta. However, after the disease has been present for a few years, extensive depigmentation may develop.

8. Neoplastic. As mentioned previously, severe chronic illness with neoplasm often is associated with hyperpigmentation.

In acanthosis nigricans, pigmented verrucous excrescences occur in the axillas and other body folds.[63] (Fig. 10B.) Acanthosis nigricans is divided into benign and malignant types. Although the dermatosis itself is benign, the so-called malignant type is associated with adenocarcinoma, particularly of abdominal organs. Benign acanthosis nigricans begins at birth, in childhood or at puberty. The malignant type may begin at any age and is preceded, accompanied or followed by an adenocarcinoma. The dermatologic findings are the same in both types. The relationship of these changes to malignancy has not been elucidated.

A few patients with melanoma develop generalized dark blue hyperpigmentation resembling that of argyria.[64] This coloring represents melanin in the dermis which appears blue when viewed from the surface of the skin. The tumor produces large amounts of 5,6-dihydroxyindole,



10A 10B 10C

FIG. 10. A, hyperpigmentation in a seventeen year old boy with chronic atopic dermatitis. B, malignant acanthosis nigricans in a twenty-eight year old woman. C, melanoma.

an unstable substance which is rapidly oxidized, even in the absence of tyrosinase, to melanin.

9. Unclassified Factors. Both hyperpigmentation and hypopigmentation occur in patients with scleroderma. The reasons for these changes remain obscure.

The skin discoloration in hemochromatosis is characteristically bronze. Often there is a slate-blue or metallic cast like argyria. The brown pigmentation represents increased amounts of melanin in the epidermis and the metallic color is due to hemosiderin in the dermis. Melanin and iron can be seen microscopically with differential staining. Both iron and copper are deposited in the skin as part of the metabolic disturbance. Because these metals bind sulfhydryl groups, thus releasing the inhibition of tyrosinase, melanin formation is increased. In addition, hyperpigmentation may result from adrenal insufficiency or cirrhosis of the liver occurring as a complication of hemochromatosis.

It is often difficult to obtain good color matches in skin grafting. Sometimes the graft is lighter than the surrounding skin; in other patients the graft may be darker even though similar donor and recipient sites were used. (Fig. 11A and 11B.) While the basis for these changes is not known, it would be of interest to determine the influence of melanocyte population density on the resulting color of the graft.

In polyostotic fibrous dysplasia the following triad of abnormalities may occur: (1) disseminated but not generalized bone lesions, usually unilateral and segmental in distribution, (2) endocrine dysfunction associated with precocious puberty in females, and (3) cutaneous pigmentation consisting of macules which vary greatly in size, tend to be of segmental distribution and are more extensive on the side of the bone lesions. They may be café au lait spots. It was stated that these lesions more so than those in neurofibromatosis were of irregular contour like the rugged "coast of Maine" whereas the café au lait spots of neurofibromatosis were described as being smooth-bordered like the "coast of California."[86] However, in a comprehensive study of neurofibromatosis which appeared recently it was shown that the configuration of the café au lait spots is variable and of no diagnostic significance.[53] Buccal pigmentation may occur. The etiology of the hyperpigmentation is not known but it may be neurogenic.

Intestinal polyposis consists of polyps distributed throughout the gastrointestinal tract, particularly the jejunum, associated with pigmentation of the buccal mucosa, lips, face and fingers. Pigmentation is more marked on the lower lip than the upper and more marked on the interior surface than the exterior. The pigmented lesions are macules, 0.2 mm. to 5 mm. in diameter, ranging in color from light brown to

11A 11B

FIG. 11. A, hyperpigmented skin graft. B, hypopigmented skin graft.

deep blue-black. Clinically, they appear to be junction nevi or lentigines and are observed first in childhood. The syndrome is inherited as a simple Mendelian dominant.[87]

MELANOMAS

The term melanoma indicates a malignant growth so the prefix 'malignant' need not be appended. Because melanocytes are derived from neural rather than epidermal or mesodermal structures the names melanocarcinoma and melanosarcoma are inaccurate. Melanomas have been found in most animals; they are relatively common in old gray horses. In some fish, gray horses and other animals melanomas are transmitted genetically. This is not the usual case in human beings; only once were melanomas of the skin reported in more than one member of a family, although there have been four reports on melanomas of the eye in families.[65]

Approximately 90 per cent of melanomas arise in persons over thirty years of age.[66,67] They occur with equal frequency in both sexes. The incidence of melanomas is two to four times as great in white persons as in Negroes. There is a general feeling that the incidence is greater and the course more rapid in persons of light complexion who do not tan but burn or freckle.

Melanomas have been reported in albinos only twice.[68,69] In one case the tumor arose from a pre-existing non-pigmented nevus and the sites of metastases remained non-pigmented. In the other a pigmented tumor arose from the eye.

Melanomas are rare in children. However, a fatal outcome may occur at any age.[70] Two cases were reported in which primary melanomas originated prenatally and subsequently caused death of the infants.[71,72] Two other infants died of metastases from melanomas in the mother.[73,74]

In adults the melanoma is the commonest malignancy of the eye and metastatic melanoma is the commonest tumor of the heart. Pregnancy increases the growth rate of melanomas.[75]

Subungual melanomas occur with equal frequency on the hands and feet. However, they are more common on the thumb than on all other fingers combined and more common on the great toe than on all other toes combined. Nearly seventy cases of melanomas originating in the meninges have been described.[76]

Approximately 50 per cent of melanomas arise from pre-existing nevi.[66,77,78] In almost all instances it is the junctional and compound nevi which give rise to melanomas. Melanomas seem to come from nevi which have been subjected to pressure, trauma or sunlight. For example, melanomas have been known to develop in nevi following a hypodermic needle prick, chicken peck, vaccination and ice-pick stab.[79–82] Nevi of the face, genitalia, feet and nail bed are most likely to undergo trauma. In many cases a lesion is malignant prior to trauma or cauterization. Since more than 10 per cent of the population have some type of nevus on the palms and soles, it is not practical to excise all these lesions. The distribution of melanomas corresponds to the sites at which the nevi are most abundant, are subjected to trauma or are exposed to sunlight. In the distribution of melanomas[83] the percentage is as follows: trunk, 24; head and neck, 22; leg, 18; sole, 9; arm, 9; eye, 5; genitalia, 3; subungual, 3; oronasal and esophageal, 2; anorectal, 2; palm, 1, and primary site unknown, 2 per cent.

Melanomas are responsible for approximately 1 per cent of deaths caused by malignant tumors. Twenty-five per cent of deaths due to melanoma occur within the first year of the disease, 62 per cent between one and five years and 13 per cent after the tumor has been present more than five years. Approximately 14 per cent of patients with metastases to the regional lymph nodes survive five years. It is claimed that 40 per cent of patients without metastases to regional nodes survive five years. However, it is possible that not all primary lesions in this latter group were melanomas. Women tend to survive longer than men. Eye melanomas offer a better prognosis than those from other sites.[66,67,83]

Although the diagnosis of melanoma can be made clinically in certain obvious cases, microscopic examination is essential. Clinically, melanomas can simulate pyogenic granulomas, angiomas, seborrheic keratoses, nevi, basal or squamous cell carcinomas, Kaposi's sarcoma, foreign bodies, and the like. Some melanomas can be diagnosed microscopically with ease but in many cases the diagnosis cannot be made readily. Microscopically, a melanoma may show (1) an inflammatory infiltrate at the periphery of the lesion, (2) more than an occasional mitotic figure, (3) giant cells with a single bizarre nucleus, (4) marked pleomorphism, (5) general enlargement of all tumor cells and (6) tumor cells and mitoses in the epidermis.[84] Pigment may not be present.

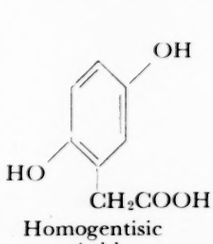
Melanoma patients often seem to have multiple primary tumors. That is, biopsy of a clinically benign nevus, distant from the primary melanoma, often shows malignant changes microscopically. Perhaps systemic changes occur in these patients so that the melanocytes appear more malignant.

The question has been raised as to whether or not it is possible to distinguish between melanomas and non-malignant pigmented lesions on the basis of the quantity or activity of tyrosinase present.[85] When large pieces of fresh melanoma tissue are incubated in solutions of tyrosine or dopa under the proper conditions, melanin is formed and the tissue turns dark. This experiment has not been done with melanomas from an albino. If tumors other than melanomas are incubated with dopa, pigment may form because dopa is oxidized readily. However, the reaction is much more specific with tyrosine.

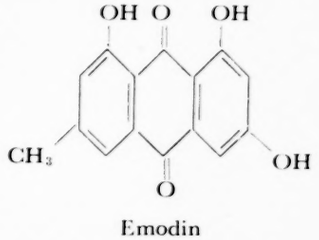
When the tyrosine and dopa reactions are carried out on thin sections of fresh melanoma tissue, microscopic examination shows that the substrates are converted to melanin. Here again the tyrosine reaction is more specific but less sensitive than that with dopa. Whether or not the total or active tyrosinase per melanocyte or melanin granule is greater in melanomas than in normal melanocytes remains to be proved.

NON-MELANOCYTE MELANIN

In this paper primary attention has been given to melanin formed from tyrosine when the principal reactions take place in the melanocyte. In considering natural pigments in microorganisms, plants and animals, it is necessary to define melanin in a broad sense as a dark pigment formed by the oxidation and polymerization of a polyhydroxy (or polyamino) aromatic compound with hydroxy or amino groups in the ortho or para positions. With this broad definition, one can say that the pigment in patients with ochronosis, phenol poisoning and melanosis coli is melanin. Ochronosis occurs in patients with alkaptonuria who have a genetic lack of homogentisase. They are unable to split the ring of homogentisic acid, which is a normal oxidation production of tyrosine in the liver, to form fumarylacetoacetic acid.[16] Homogentisic acid, a paradihydroxyphenyl compound, accumulates and is oxidized in tissues such as cartilage to a dark pigment. The oxidation probably occurs as a non-specific reaction in the presence of oxidizing systems such as cytochrome C-cytochrome oxidase.



Homogentisic Acid



Emodin

Exposure to phenol and related compounds can result in increased pigmentation of the skin. It is likely that polyhydroxy phenol derivatives are formed from phenol and oxidized to a pigment.

Melanosis of the large bowel occurs in persons who have used cascara as a laxative for long periods of time. Cascara contains emodin, an anthraquinone, which is probably oxidized in the presence of microorganisms in the colon to a black pigment that becomes attached to proteins of the mucosal wall.

SUMMARY

The mechanisms of normal and abnormal melanin pigmentation are discussed, with special reference to the cytology of melanocytes, enzymic factors concerned with melanin formation and hormonal and neurogenic control of melanocyte activity. An attempt is made to integrate these factors in order to explain clinical variations in pigmentation.

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Seminar on Carbohydrate Metabolism

Evolution of Modified Insulins in the Treatment of Diabetes Mellitus, with Special Emphasis on Insulin-Zinc Suspensions*

RANDALL G. SPRAGUE, M.D. *and* RALPH A. KILBY, M.D.
Rochester, Minnesota

MULTIPLE modifications of insulin, particularly the protamine zinc, NPH and globin preparations, have been available for several years. Recently, the number of modified insulins has been further augmented by the introduction of the insulin-zinc suspensions or lente insulins. The physician must think of the effects of each modification and of certain combinations of them, not only in respect to the physiologic activity of insulin in general but also in terms of the three special dimensions of action, namely, promptness, intensity and duration. With so many variables to be considered the insulin situation is inherently confusing and a brief review, with emphasis on the new insulin-zinc preparations, seems to be in order.

The insulin-zinc suspensions have become available at a time when there is no pressing need in this country for such modifications. Physicians already have at their disposal preparations which, either singly or in combinations, have timing characteristics which fit reasonably well the needs of virtually all diabetic patients under almost all circumstances. Now, however, there is a plethora of modified insulins, with considerable duplication of the effects of certain preparations. As Colwell[1] has pointed out, had the lente modifications been discovered some twenty years ago it seems doubtful that any of the protein depot insulins ever would have emerged at all, for the newer preparations promise to provide all the gradations of timing of action that previously were offered by protamine zinc, NPH and globin insulin, alone or in mixtures with soluble insulin.

Nevertheless, the lente insulins are undoubtedly with us to stay and probably offer certain advantages over their predecessors. In this article an effort will be made to review the background for the development of these modified insulins, to comment briefly on their clinical use, and to indulge in some speculations regarding the future of modified insulins.

SOME GENERAL OBSERVATIONS

It is not always recognized that there is a great variability in response to treatment among diabetic patients who require insulin. The reasons for this variability are not well understood. Perhaps variations in response indicate that there are different forms of diabetes, different etiologic factors, or possibly only differences in the intensity of the disease. In any event, it is important to be aware of the inherent ease or difficulty of therapy in different patients before one chooses a program of insulin administration for any given patient, and particularly before one passes judgment on the scope of usefulness of any modification of insulin which is to be employed in a large group of patients. Hallas-Møller and his associates[2,3] have recently presented extensive data on the behavior of the blood sugar in response to various insulins in sixty-five patients with severe diabetes. Among other things, their data re-emphasize the varia-

* From the Mayo Clinic and Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

tions in response of different patients to the same insulin.

It should also be recognized that blood sugar curves, even if obtained under the most carefully controlled conditions, are not specific indexes of the action of the insulin under study but rather are an expression of the interaction of a number of factors. These include, in addition to the preparation of insulin employed, the patient as a whole, the type of diabetes which affects him, his diet, his physical activity or lack of it, his emotional state, the technic and site of injection of insulin, and perhaps other factors. In the brittle or unstable diabetic patient there may be variable and unpredictable alterations in some of these factors from time to time. Clinical experience has shown that no preparation of insulin can be expected to overcome all sources of variation in the behavior of this type of diabetes. It has often been stated that the ultimate goal in the development of insulin is an "automatic" insulin, that is, a preparation the rate of absorption of which from the site of subcutaneous injection will be determined by the level of the blood sugar or some other index of metabolic need. Unfortunately, there is no immediate prospect for the development of an insulin with such a high order of intellect and the physician must therefore make the best possible use of insulins which are currently available.

Any discussion of the niceties of action of insulin in clinical practice must be preceded by consideration of the question, Is control of diabetes important? This is not the place for a detailed discussion of this vital and controversial question. However, there is a growing impression, and some moderately convincing evidence, that poor control of sugar in the blood and urine may be a factor in the development of the degenerative complications of diabetes and, conversely, that good control of sugar in the blood and urine tends to prevent or delay the development of such complications. In any event, efforts to control diabetes seem to be advisable until such time as control has been conclusively shown to be unimportant. The discussion which follows is therefore predicated on the assumption that, in the present state of knowledge, control of diabetes is desirable.

EVOLUTION OF THE MODIFIED INSULINS

If one concedes that control of diabetes is a worth while objective, then the timing characteristics of the insulin or combination of insulins employed in each case assume considerable importance. Obviously, precise control cannot be achieved with a reasonably simple program of insulin administration unless the timing of the action of the insulin is well fitted to the needs of the individual patient.

The shortcomings inherent in the quick, intense and brief action of soluble insulin (regular and crystalline) and in the slow, weak and prolonged action of protamine zinc insulin are now generally appreciated. Intermediate-acting modifications were developed in response to a need for preparations the timing characteristics of which would be more consonant with the requirements of the majority of diabetic patients. The first such modifications which found wide use were mixtures of protamine zinc insulin and soluble insulin. The action and clinical use of such mixtures were thoroughly studied and described by Colwell and his collaborators.[4–6] Mixtures, when prepared extemporaneously in the syringe, provided necessary flexibility of quick and slow action for varying needs. They were used extensively in our own practice[7,8] and that of many others but obstacles were presented by their inconvenience and the difficulties which some patients experienced in mastering their use.

The combining of quick and prolonged actions in one insulin with intermediate timing characteristics was a step in the right direction. The first such insulin available for general use in this country was globin insulin.[9] Although controlled studies[10,11] showed its timing characteristics to be essentially similar to those of 2:1 mixtures of soluble insulin and protamine zinc insulin (the most commonly used proportions) and to those of NPH insulin, some observers gained the clinical impression that the action of a single morning dose of globin insulin was a little too short to maintain control of some cases of severe diabetes throughout the succeeding twenty-four hours.

NPH or isophane insulin[12] accurately reproduced the action of 2:1 mixtures[11,13–17] and promptly gained wide acceptance in this country. In our own practice, and that of many others, the majority of patients who had been under treatment with mixtures were changed to NPH insulin when the opportunity presented itself. Generally speaking, the results were good. When necessary, the timing characteristics of NPH insulin could be altered in the direction of greater speed by the admixture of small amounts of soluble insulin. For the few patients who

required a less intense insulin action during the day than was provided by NPH insulin, either the admixture of protamine zinc insulin with NPH insulin (which was rarely done) or the use of mixtures of soluble and protamine zinc insulin in a ratio of less than 2:1 was possible.

Thus insulins and combinations of insulins that fitted the needs of virtually all diabetic patients were at hand. Soluble insulin continued to be available for use in emergencies. NPH and globin insulin were well adapted to the day-by-day needs of most diabetic patients. The action of either could be accelerated, when necessary, by the addition of soluble insulin. Mixtures of protamine zinc insulin and soluble insulin could be adjusted to provide any other desired timing of insulin action. Insulin allergy was an infrequent problem. One could reasonably ask the question, What real need is there for additional insulin modifications?

It is apparent that if one thinks only in terms of the timing characteristics of insulin action, there was no pressing necessity for the introduction of the lente modifications. However, as will be brought out, these new modifications may provide slight advantages over other preparations, namely (1) a greater degree of "purity" owing to the absence of such modifying agents as protamine and globin, (2) a possibly diminished incidence of insulin allergy and (3) a possible ultimate reduction in the number of insulins from which the harried physician must choose.

The chemical characteristics of the currently available insulin modifications are shown in Table 1. It will be noted that the essential constituents of all the modifications prior to the lente insulins were insulin, zinc, a buffer (except in the case of globin insulin) and a modifying agent in the form of either protamine or globin.

THE LENTE INSULINS

Probably the most unusual aspect of Hallas-Møller's[18,19] discovery of the insulin-zinc modifications was his astute observation that the simple omission of phosphate or citrate buffer, and the employment of acetate buffer instead, enabled relatively small amounts of added zinc ion to exert a depressing effect on the solubility of insulin and hence on the rate of absorption of the hormone from sites of injection. Since the affinity of zinc for phosphate and citrate is greater than for insulin, the presence of these buffering agents effectively prevents or impedes the combination of zinc and insulin. Scott and Fisher[20] had shown in 1935 that the addition of rather large amounts of zinc to solutions of insulin containing phosphate buffer caused a pronounced prolongation of the action of the hormone when injected subcutaneously in rabbits. Rabinowitch and associates[21] had demonstrated the prolonged action of such preparations in diabetic patients. However, the amounts of zinc which it was necessary to add were large (400 to 1,000 mg. per 1,000 units) and the preparations were not considered suitable for clinical application.

TABLE 1
CONTENT OF ZINC, BUFFER AND MODIFYING PROTEIN OF VARIOUS INSULINS

Insulin	Description	Zinc Content (mg. per 1,000 units)	Buffer	Modifying Protein
Short Action				
Amorphous	Solution	0–0.4	None	None
Crystalline	Solution	0.16–0.4	None	None
Semilente	Suspension	2–2.5	Sodium acetate	None
Intermediate Action				
NPH	Suspension	0.16–0.4	Sodium phosphate	Protamine
Globin	Solution	2.5 –3.5	None	Globin
Lente	Suspension	2 –2.5	Sodium acetate	None
Prolonged Action				
Protamine zinc	Suspension	2 –2.5	Sodium phosphate	Protamine
Ultralente	Suspension	2 –2.5	Sodium acetate	None

Hallas-Møller's work elucidated a new concept of the chemical relation of zinc and insulin. It conclusively demonstrated that the solubility of insulin can be lowered and its action prolonged simply by the addition of zinc under appropriate chemical conditions, without recourse to protamine or comparable basic substances. In the lente insulins the concentration of zinc, although remarkably low, is nevertheless approximately ten times the amount necessary for the formation of soluble zinc-insulin crystals. (Table 1.) By careful adjustment of the pH a number of crystalline and amorphous preparations can be produced. The crystalline compounds are much more insoluble than the amorphous, and therefore much longer-acting.

Lente Preparations. Of the many different types of insulin-zinc suspensions which can be prepared under different chemical conditions, three have now had clinical trial. The name given to each utilizes the basic term "lente" to indicate slow action.

1. *Semilente*, which is a suspension of zinc-insulin crystals in an amorphous state. Its action is intermediate between the actions of soluble insulin and NPH insulin in terms of promptness, intensity and duration.

2. *Ultralente*, which is a suspension of zinc-insulin crystals of a size of 10 to 20 μ. Its action is slow, prolonged and of low intensity, similar to that of protamine zinc insulin.

3. *Lente*, which is a mixture of the foregoing two preparations in proportions of 30 per cent semilente and 70 per cent ultralente. As already indicated, the timing of its action is almost precisely the same as that of NPH insulin.

Inasmuch as the lente modification or mixture is the only one currently available on the market in this country, and the one which has had the most extensive clinical trial here and elsewhere,[2,3,22–65] most of the comments which follow will be limited to this preparation. In addition, some predictions of the ultimate place of semilente and ultralente modifications, which no doubt soon will be available, will be made.

Experience to date indicates that lente insulin and NPH insulin can usually be used interchangeably. In an occasional case the action of lente insulin has seemed a little less intense and more prolonged than that of NPH insulin. Generally speaking, however, it is our current impression that one must look elsewhere than timing characteristics for advantages of lente insulin over other preparations with intermediate action.

Is the "Purity" of Lente Insulin an Important Advantage? Lente insulin, containing as it does no modifying protein, fits in with a developing trend toward purity in drugs and hormones for clinical use. That such a trend actually exists is attested by the gradual replacement in clinical medicine of such agents as digitalis leaf by pure cardiac glucosides, relatively crude adrenocortical extracts by synthetic steroid hormones in crystalline form, plant antispasmodics such as belladonna by a variety of synthetic antispasmodics, and many similar examples. At present, it is difficult to assess the importance of the purity of lente insulin. It has been speculated that prolonged administration of protamine in the form of protamine zinc insulin or NPH insulin might be a factor in the development of the degenerative complications of diabetes but there is actually little or no basis for this supposition. With the possible exception of the incidence of insulin allergy, which is low with any insulin, there are no good yardsticks for the appraisal of the importance of the purity of lente insulin.

Insulin Allergy. The literature on lente insulin to date suggests that its use is probably attended by a lower incidence of local and general sensitivity reactions than in the case of insulins containing modifying proteins. This is what would be anticipated, for protamine and globin are undoubtedly responsible for some of the sensitivity reactions to insulins containing these substances. However, it seems likely that any insulin made from animal pancreas, no matter how pure it might be, will be antigenic in a small number of diabetic patients. Hallas-Møller and associates[18] and others (Murray and Wilson,[32] Nabarro and Stowers,[33] Jersild and associates,[22] Lawrence and Oakley,[24] and Oakley[31]) have apparently not observed any instances of insulin allergy among patients treated with lente insulin. Their reports were based mainly on experience with the Danish preparation. Subsequent reports by some of these investigators and others (Armstrong and Lloyd[48] Greenhouse,[60] Holcomb and associates,[45] Peck and associates,[47] Gurling and associates,[65] Stowers and Nabarro[59]) have indicated that the British and American lente insulins are capable of inducing sensitivity reactions. It appears that an insufficient number of cases in which lente insulin from various commercial sources has been used and which have been carefully observed with respect to the development of insulin allergy have yet been reported to provide an estimate of the incidence of sensitivity reactions.

Modification of the Timing Characteristics of Lente Insulin. Because of its intermediate timing characteristics, lente insulin, like NPH insulin, is undoubtedly a suitable preparation for a high proportion of all diabetic patients who require treatment with insulin. There are, however, a few patients for whom its action is either too slow and prolonged or too rapid and short. For these patients the action of lente insulin must be either accelerated and shortened or retarded and prolonged.

Limited experience to date indicates that acceleration of action can be achieved by mixing

small amounts of soluble insulin with lente insulin. Apparently the independent actions of the two insulins are preserved in the mixture, provided that the amount of added soluble insulin is small. Colwell[1] has cautioned that the addition of large amounts of soluble insulin to lente insulin may alter the size and form of the insulin-zinc crystals in an unpredictable manner, and therefore the rate of release of the hormone from sites of injection. In other words, not enough is yet known about the action of mixtures of soluble and lente insulin in varying proportions to warrant final statements regarding their clinical application.

TABLE II
USE OF LENTE INSULINS AT HVIDØRE HOSPITAL, COPENHAGEN, DENMARK (REPORT OF JULY, 1954)*

	Patients	Per cent
Adjusted on the lente insulins (Average daily dose, 40 units)	1,030	100†
Dismissed with one injection daily	990	96†
Dismissed with two injections daily	40	4†
Types of Insulin Employed in the Group Receiving One Injection		
Semilente alone	0	0‡
Lente-semilente mixtures	93	9‡
Lente alone	790	80‡
Lente-ultralente mixtures	100	10‡
Ultralente alone	7	1‡

* Data from Hallas-Møller.[66]
† Per cent of 1,030.
‡ Per cent of 990.

For the future, a more promising method for tailoring the timing of insulin action to the needs of individual patients may be the preparation of mixtures containing semilente and ultralente insulins in varying proportions. The two insulins can be mixed in any desired proportion without altering the chemical or physical properties of either. Ultralente and semilente in a 70:30 proportion (lente insulin) fit the needs of a high proportion of all patients who require insulin. It should be possible to regulate patients who require a more rapid insulin action during the day on mixtures containing a higher proportion of semilente insulin, while the few who require a slower action can be regulated on mixtures containing a higher proportion of ultralente insulin. Hallas-Møller has recently reported on the frequency with which lente-semilente and lente-ultralente mixtures have been employed in the treatment of a large number of diabetic patients in Denmark. (Table II.)

The desired proportion of semilente and ultralente insulin in a mixture can be obtained either (1) by mixing semilente and ultralente insulin or (2) by mixing lente with either semilente or ultralente insulin. Careful education of the medical profession, to say nothing of diabetic patients, will be necessary if confusion is to be avoided in the preparation of such mixtures.

OBSERVATIONS ON 100 CONSECUTIVE PATIENTS TREATED WITH LENTE INSULIN

A review of the records of 100 consecutive ambulatory diabetic patients who have been treated with lente insulin at the Mayo Clinic since January 1, 1955, tends to confirm many of the foregoing observations.* Most of the 100 patients had not previously been under our care and came to us on a variety of different programs of insulin administration. The principal reasons for the decision to treat them with lente insulin were as follows: (1) Inadequate control of daytime glycosuria and occurrence of nocturnal hypoglycemic reactions during treatment with protamine zinc insulin alone or with mixtures of protamine zinc insulin and soluble insulin which contained too high a proportion of protamine zinc insulin (twenty-four patients). (2) Greater convenience of one daily dose of lente insulin as compared with mixed doses of protamine zinc insulin and soluble insulin (five patients). (3) Inadequacy or inconvenience of multiple doses of soluble insulin (four patients). (4) Daytime reactions and inadequate overnight control during treatment with globin insulin in single morning doses (four patients). (5) Local allergic reactions to NPH insulin, protamine zinc insulin or soluble insulin (six patients). (6) Patients arbitrarily changed from NPH insulin or protamine zinc insulin to lente insulin for no clear-cut reason (sixteen patients).

* Supplies of lente insulin for preliminary studies were kindly provided by the Lilly Research Laboratories, Indianapolis, Ind.

(7) Patients not previously treated with insulin and arbitrarily chosen for treatment with lente insulin (twenty-six patients). (8) Patients already under treatment with lente insulin when first seen (fifteen patients).

It will be noted that the reasons for the employment of lente insulin in preference to other intermediate-acting insulins were usually not of a compelling nature. The principal gains from the change to lente insulin, if any occurred, were increased convenience and improvement of control. In most instances one or both of these advantages could as well have been achieved by the use of one of the other intermediate-acting insulins. For example, patients whose previous control with protamine zinc insulin alone had been inadequate could have been treated as well with one of the other intermediate-acting preparations as with lente insulin. There was no discernible advantage in changing from NPH to lente insulin. In a few instances, lente insulin seemed to provide better control than globin insulin by virtue of a less intense and more prolonged action.

Observations in Six Cases of Insulin Allergy. As already indicated, six of the patients who were treated with lente insulin had experienced local allergic reactions to the preparation which they had previously employed. None of these derived complete relief by the substitution of lente insulin. Two felt that their local reactions were as intense as before, while in the remaining four patients slight to marked diminution in the intensity of the local reaction was reported. Among the latter four patients was one with insulin atrophy. Subsequent observation of this patient, however, indicated that lente insulin was producing mild but definite atrophy as well as local sensitivity reactions.

Mixtures of Lente and Soluble Insulin. Such mixtures were employed in seven cases. In each of these the ratio of units of lente to units of soluble insulin was high, the lowest ratio being 7:3. As far as could be determined, the use of relatively small amounts of soluble insulin produced a satisfactory acceleration of insulin action without noticeably altering the depot characteristics of the lente insulin. The possibility exists, however, that employment of larger amounts of soluble insulin in such mixtures, with consequent alteration of pH, might change the character of the crystals of lente insulin and therefore their depot effect.

The Use of Two Doses of Lente Insulin. It has long been our belief that improved control can be achieved in a small group of patients with unstable diabetes by the use of two daily doses of intermediate-acting insulin. It has been our practice to administer the two doses before breakfast and before supper; others have administered the evening dose at bedtime. We know of no data which demonstrate which of these methods is to be preferred.

In the present series of 100 patients five were treated with two daily doses of lente insulin. All five had unstable diabetes which had not been well controlled on any program involving a single morning dose of insulin. The morning doses were from two to six times as large as the evening doses. In one instance the morning dose was a mixture of lente and soluble insulins. In the other five instances lente insulin alone was employed.

The advantages of the use of lente and other intermediate-acting insulins in this manner in some cases of unstable or brittle diabetes seem to outweigh the disadvantage of two daily injections of insulin. In our opinion, it is a method of treatment which deserves more extensive application to severe diabetes than it now has.

THE FUTURE PLACE OF INSULIN-ZINC SUSPENSIONS

For the many physicians who treat only a few diabetic patients and who find it difficult to focus their attention on the finer subdivisions of the insulin field, the addition of three new modifications of insulin to those already available is more likely to be confusing than helpful. From this point of view, the introduction of semilente, lente and ultralente insulin is to be viewed with some misgivings, especially since their advantages over existing preparations are not great and, indeed, in the individual case will usually be difficult to recognize or demonstrate.

On the other hand, with the passage of time it is not unlikely that the new preparations, by substituting for and replacing existing preparations, may help to bring about a reduction in the number of insulins from which the physician must choose. Insulin manufacturers might well do what they can to hasten the replacement of some of the existing preparations with the lente insulins. Certainly the new insulins will make it possible for patient and physician to obtain any desired timing of insulin action either by using lente insulin alone or by using semilente and ultralente insulin in proper proportions. As Colwell[1] has pointed out, it remains to be determined whether predictability of action and consistency of response to these insulins will be

greater than in the case of the protein-precipitated insulins. If the insulin-zinc suspensions are not inferior in this respect, and there is no reason to anticipate that they will be inferior, there is no compelling reason why they should not eventually take the place now held by the protein-precipitated insulins in the therapy of diabetes. They will not, of course, replace soluble insulin for the treatment of emergencies such as diabetic acidosis.

SUMMARY

For some time the physician who is concerned with the treatment of diabetes has had at his disposal good preparations of insulin with timing characteristics which are suitable for almost all diabetic patients under almost all circumstances. In the past fifteen years there has been increasing appreciation of the fact that insulins with timing characteristics intermediate between those of soluble insulin and protamine zinc insulin provide excellent replacement therapy for the great majority of patients who require insulin. These preparations include NPH insulin, globin insulin and appropriate mixtures of soluble insulin and protamine zinc insulin.

While one's first reaction to the introduction of the new insulin-zinc suspensions is likely to emphasize the confusion resulting from the availability of additional insulins, it is not unlikely that the new preparations, by virtue of their freedom from modifying proteins and their probable adaptability to the needs of almost all diabetic patients, may eventually substitute for and replace all of the existing preparations except regular insulin and crystalline insulin. Such a course of events, while it might take a long time, could be accelerated by the insulin manufacturers and would simplify a confusing situation.

Observations on 100 consecutive patients with diabetes mellitus treated with lente insulin are presented.

With the introduction of the insulin-zinc suspensions, it is difficult to conceive of any further important practical developments in the field of injectable modified insulins, short of an "automatic" insulin whose rate of release from the site of injection would be determined by the level of the blood sugar. We know of no prospect for the development of such an insulin in the foreseeable future. At present the most fruitful field for improvement of the treatment of diabetes is the clinical use of currently available insulins to the best possible advantage of the patient.

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The Problem of Degenerative Vascular Disease in Diabetes*

HENRY T. RICKETTS, M.D.
Chicago, Illinois

VASCULAR disease is generally recognized as the most important problem in clinical diabetes today. Seventy per cent of diabetic deaths in Joslin's clinical cases[2] and 47 per cent in Bell's[3] postmortem series were caused by arteriosclerosis. By comparison, 30 per cent of deaths in the general population are ascribed to this cause.[3] What is more striking, indeed appalling, is the high incidence of vascular degeneration in young patients with long-standing diabetes. White and Waskow,[4] for example, found that of 200 such patients whose diabetes had begun in childhood and who had survived for twenty years or more, 92 per cent were so affected. It is apparent that senescence plays a far lesser role than does diabetes itself, or some factor associated with it, in the vascular disorders of this disease.

THE LESIONS AND THEIR CLINICAL EFFECTS

The clinically important vessels involved are for the most part the medium-sized arteries of the myocardium, lower limbs and brain; the arterioles, especially of the kidney; and the capillaries of the renal glomeruli and retina.

Atherosclerosis and Arteriolosclerosis. The characteristic lesion of the medium-sized arteries in diabetes is atherosclerosis.[5] This term is used to describe focal thickenings of the intima which contain greater or lesser amounts of lipids and, in the later stages, calcium. It is these lesions that are responsible for most of the occlusive vascular phenomena which constitute the largest single cause of death in the diabetic population.

Arteriolosclerosis of the kidney, affecting particularly the afferent and efferent vessels of the glomeruli, is marked by hyalinization of the arteriolar wall. Although often observed in other conditions, such as chronic glomerulonephritis and essential hypertension, it occurs with greater frequency and with much greater intensity, according to Bell,[6] in long-standing diabetes, particularly in younger patients with hypertension.

Intercapillary Glomerulosclerosis. Notwithstanding the importance of disease of the arterial system, which after all occurs commonly enough in non-diabetic persons, disease of the capillaries has received increasing attention because certain forms of it are almost uniquely an accompaniment of the diabetic state.

Characteristic alterations of the renal glomeruli were described in association with diabetes in 1936 by Kimmelstiel and Wilson,[7] who called the condition "intercapillary glomerulosclerosis." Their findings were quickly and widely confirmed but there has been disagreement as to whether the lesions arise between the glomerular capillaries, as the original term implies, or in the basement membrane of the capillary itself. At any rate there occurs, probably as the earliest change, an axial thickening in the supporting structure of the glomerular tuft. This has been referred to as the diffuse form of the disease,[6] and it may progress in extent and severity without the development of nodules. In many cases, however, the process goes on, by steps as yet unknown,[8] to the formation of spheroid nodules resembling hyaline. These stain pink with hematoxylin and eosin and readily accept the periodic acid-Schiff reagent, a property which suggests that they contain a carbohydrate, probably a mucopolysaccharide.[9] That they are not composed of the usual hyaline is indicated by the fact that they are more resistant than this material to digestion with trypsin.[10] Some of the nodules are laminated, and many of them contain lipids, according to Wilens,[11] who has proposed that the deposition of fatty substances may be primary in their pathogenesis. Dilatations of the capillaries,[12] which have been

* For a more detailed treatment of this subject, as well as a more comprehensive bibliography than this article provides, the reader is referred to the excellent review of LeCompte.[1]

likened by Friedenwald[13] to the microaneurysms of the retina, have been described.

The diffuse type of glomerular involvement, while seen far more commonly in diabetes than in other conditions, does not seem to be specific for that disease for similar lesions are found in some cases of glomerulonephritis[6,14] and in aged individuals.[15] The nodular type, however, particularly when severe, is for all practical purposes confined to the kidneys of diabetic patients.[10]

The frequency with which intercapillary glomerulosclerosis is found among diabetics at necropsy has been variously reported to be from 20[16] to 64[17] per cent. This variation is doubtless explained in large part by differences in the stringency of the histologic criteria adopted for diagnosis.

The clinical manifestations of intercapillary glomerulosclerosis, when fully developed, consist of albuminuria, edema and hypertension. Retinopathy, which is basically "diabetic" in appearance and origin but may have "hypertensive" elements, is the rule. Doubly refractive fat, both in the free form and in casts, is usually found in the urine.[18] Anemia is common, hypoproteinemia less so, and azotemia appears with the advent of renal insufficiency.

Considering the difficulties of fixing the time at which the renal disease actually begins, it is safe to state that its course is relatively slow. Henderson and his collaborators,[14] in a review of postmortem records, found that patients survived for months to years after the syndrome had been recognized, whereas the terminal illness of patients with glomerulonephritis was of one to four months' duration. The chronology of events in thirteen fatal cases of "diabetic nephropathy" (*vide infra*) has been summarized by Wilson, Root and Marble as follows:[19] In terms of average patient age, diabetes began at 14.2 years, "nephropathy" at 22.0 years and death occurred at 33.0 years. Among the sixty-one cases studied by Henderson[14] death was caused by cardiovascular disease in 52.5 per cent and by renal insufficiency in only one case. It is important to realize, however, that the average age of these patients at death was sixty years. In studies of younger patients based on clinical records, Root[20] found "nephritis" to be the cause of death in 30 per cent and heart disease in 32 per cent of 531 patients with onset of diabetes prior to thirty years of age and duration over fifteen years; and Joslin and Wilson[21] report death from "nephritis" in 52 per cent of 135 juvenile diabetic patients who died between 1944 and 1949. Thus renal disease seems to account for a higher proportion of deaths as age at death decreases. It should be noted that the term "nephritis," and later "nephropathy," (as used by the Joslin group) includes nephrosclerosis and pyelonephritis as well as intercapillary glomerulosclerosis. This renders impossible a strict comparison of their clinical data with those on only intercapillary glomerulosclerosis obtained at necropsy. Such terminology, however, seems unavoidable in view of the lack of complete correlation between clinical manifestations and the histologically proved presence of the Kimmelstiel-Wilson lesion. Biopsies of the kidney during life,[22,23] as well as postmortem studies,[1,24] reveal that not all patients with this lesion exhibit symptoms and not all patients with suggestive symptoms have the lesion.

Zubrod, Eversole and Dana[25] have made the interesting observation that diabetes tends to be, or become, mild and acidosis rare in individuals with proved intercapillary glomerulosclerosis. However, the fact that younger patients with long-term diabetes of great severity—a group but scantily represented in that study—have a high incidence of renal disease prevents acceptance of the authors' conclusions as being generally applicable. They have indeed been challenged by Runyan and co-workers[26] who reported in a similar study of necropsy and clinical records that patients with and without the specific glomerular lesion experienced much the same changes in their insulin requirements as the illness became terminal, approximately 26 per cent of both groups needing more, 38 per cent less and 34 per cent the same amount of insulin as compared with their earlier requirements. The latter authors also found that twenty-five episodes of acidosis had occurred in the fourteen patients with specific renal disease and eleven episodes in the nine patients without it. They have provided a probable explanation for the diminished insulin requirement in some cases by following the dietary histories of five living diabetic patients during the onset and progression of kidney disease and demonstrating a marked diminution of food intake. They suggest that failure to lose weight, cited by Zubrod as evidence against a decreased consumption of food, may be due to progressive edema.

Diabetic Retinopathy. Retinopathy comprises the other great class of capillary lesions in diabetes. Its earliest manifestation is the appear-

ance of tiny saccular dilatations arising from the venous side of the capillary bed in the inner nuclear layer of the retina. These microaneurysms, as they have been termed by Ballantyne and Lowenstein,[27] vary in size from 30 to 90 μ in diameter, hence many of them can be seen with the ophthalmoscope. Some of them are undoubtedly what used to be described as "punctate hemorrhages." While the latter certainly occur, and definite distinction is often difficult during life, the microaneurysms have borders that are sharply circumscribed instead of fuzzy and they may be seen in exactly the same place for months or years instead of undergoing absorption and scarring. The walls of some are thin and presumably rupture easily, while others have thick walls that appear to contain hyaline, an observation which suggested to Friedenwald[13] that these aneurysms and the glomerular nodules of the Kimmelstiel-Wilson lesion may be chemically, and even pathogenetically, related. In addition to the capillaries, the veins are frequently involved, being rather uniformly dilated in the early stages and later showing marked tortuosity and beading. Sclerosis of the arteries also occurs but is less specific and less striking than the venous lesions. Disease of both capillaries and veins leads to retinal hemorrhages which vary in size from minute to massive, sometimes invading the vitreous. Exudates, which appear "hard" and yellowish in contrast to those of hypertension and glomerulonephritis, are of common occurrence. Extensive growth of new vessels (retinitis proliferans) and scar formation may result in retinal detachment.

As in the case of intercapillary glomerulosclerosis, retinal microaneurysms are not entirely specific for diabetes but they are seen far more commonly in this condition than in others.[28] They have been reported in cases of severe hypertension, in patients with glaucoma and even in supposedly normal individuals,[29] and have been observed both experimentally and clinically in occlusion of the central vein of the retina.[30] What role, if any, venous stasis plays in the production of microaneurysms in diabetic persons is conjectural. Certainly they occur frequently in the absence of both arterial hypertension and retinal arteriosclerosis.[28]

Henderson and his colleagues[14] have called attention to the disturbing increase in the incidence of retinopathy among diabetic patients as revealed by a succession of studies at the Mayo Clinic. In 1921 the frequency was 8.3 per cent; in 1934, 17.7 per cent and in 1945, 30.6 per cent. These figures are for all age groups and, moreover, do not take account of the duration of diabetes which is a factor of the greatest importance in determining the development of retinopathy. It is surely, at least in part, the short duration of life, as well as of diabetes, that explains the low incidence of retinopathy in 1921, just as the much longer duration of both contributes to its high incidence in the present day.

The clinical symptoms of retinopathy vary from minimal disturbance of vision to complete blindness. The latter may occur within a few months of onset but usually the course of the disease is measured in years. The author has observed a number of patients with minimal retinopathy which has apparently remained stationary over periods up to five years. In the more severe cases secondary glaucoma is not uncommon.

The close, although not universal, association between diabetic retinopathy and intercapillary glomerulosclerosis is well established. Henderson[14] reports retinopathy in 68.8 per cent of cases in which the presence of the nodular renal lesions was proved by necropsy but in only 22.8 per cent of cases in which the absence of such lesions was so proved. This means that nearly one-third of patients with unquestionable intercapillary glomerulosclerosis had no clinically recognizable retinopathy. It must be pointed out, however, that retinopathy, or lack of it, in these cases had been determined ophthalmoscopically during life. When Ashton,[12] and later Friedenwald,[31] examined both the kidneys and the retinas of diabetic patients microscopically, no Kimmelstiel-Wilson lesions were found in the absence of retinal microaneurysms. On the other hand, the existence of retinopathy does not guarantee the presence of the renal lesions, for when the kidneys of patients with microscopically demonstrated retinal aneurysms were examined intercapillary glomerulosclerosis was found in only 58 per cent by both Ashton and Friedenwald.

The involvement of the capillaries of the kidney and retina led Ashton to a search for similar lesions in other tissues.[29] The results were negative. While increased capillary fragility has been demonstrated by the tourniquet test in patients with diabetic retinopathy,[32] structural changes in the cutaneous capillaries have not been described. Ditzel[33,34] has reported

abnormal patterns in the conjunctival vessels of living diabetic patients and, in some cases, their blood relatives. This potentially important observation awaits confirmation.

CIRCUMSTANCES AFFECTING THE OCCURRENCE OF VASCULAR DISEASE IN DIABETES

Heredity. Primary among the many questions of which our problem is composed is that of whether susceptibility to vascular degeneration is a result of the diabetic state or whether it is hereditary or constitutional, being passed on to succeeding generations along with the tendency to diabetes itself. Conceivably, both might be true, one factor reinforcing the other. If diabetes alone were responsible, one would expect to find a correlation between the frequency and severity of vascular disease on the one hand and, on the other, the duration and magnitude of the metabolic disturbances. There is in fact some such correlation and its importance is very great but it appears to fail in a significant number of cases. Vascular lesions are seen in some patients with presumably early and certainly mild diabetes and are sometimes not demonstrable in patients whose diabetes is of long standing, severe and habitually under poor control. It is these facts that have raised the question of an hereditary influence. Actually, meaningful data on this subject are non-existent so that it must remain for the present a topic for speculation.

On the other hand, there is evidence in both man and animals that diabetes *per se*, accidentally or intentionally produced under conditions which nearly or completely exclude genetic influences, sometimes leads to vascular degeneration. Lawrence[35] cites cases of this kind in which diabetes was brought on by gross pancreatic disease, and Sprague[36] has described a patient in his early forties with a negative family history in whom diabetes appeared during the course of chronic relapsing pancreatitis, followed by neuritis after seven years, diabetic retinopathy after ten years and the manifestations of intercapillary glomerulosclerosis after eleven years of diabetic symptoms. Hudson[37] has reported retinal microaneurysms in a fifty year old diabetic patient with hemochromatosis of fifteen years' duration. The experimental induction of diabetes has been followed by sclerosis of the aorta[38] and coronary arteries[39] in dogs and by lesions resembling intercapillary glomerulosclerosis in dogs[40,41] and rats.[42,43] No claim has been made in any case that these lesions were identical with those found in man but the observations remain highly significant nevertheless.

Sex. Coronary disease among non-diabetic persons occurs several times more frequently in males than in females. Diabetes not only increases by two- or threefold the over-all incidence of this disorder but also eliminates the sex difference, so that the ratio of males to females experiencing myocardial infarction is approximately one to one.[44–47] The same is true for arteriosclerosis of the legs, which among non-diabetic persons is observed predominantly in males[48,49] but among diabetic persons, as evidenced by gangrene, occurs as often in women as in men.[47,50]

Although some authors have reported no sex difference in the frequency of "chronic renal disease"[47] and "nephritis"[51] among diabetic individuals at necropsy, the majority who have confined their studies to intercapillary glomerulosclerosis have found the percentage of occurrence from one and one-half to two times as great in women as in men.[6,15,46,52]

Diabetic retinopathy seems to afflict males and females with about equal frequency.[47,53] This is surprising in view of the close relationship between retinopathy and intercapillary glomerulosclerosis and the somewhat greater predilection of the latter for women.

The Time Factor: Age of Patients and Duration of Diabetes. It is difficult to discuss the effect of age on vascular disease without considering the effect of duration of diabetes, for the latter, at any given age, is a factor more potent than any other we know, and within different age groups has different degrees of influence.

Age alone, of course, plays its own role, particularly in arterial disease. It is evident from Table 1, compiled from the report of Root and his colleagues,[44] that the incidence of coronary occlusion at necropsy is nearly four times higher in diabetic patients between forty and sixty years of age than in those under forty. The corresponding figures for non-diabetic persons, however, show a tenfold increase in the older as compared with the younger ages, indicating that advanced age is of less importance in the presence of diabetes than in its absence. Conversely, for ages under forty diabetes increases the frequency of coronary occlusion tenfold while for those over forty the increase is only fourfold. Diabetes, then, has a more profound effect on coronary disease in younger persons than in

older ones. It seems to have a similar effect on peripheral arteriosclerosis in relation to age, for Bell[50] has shown that the incidence of gangrene is 156 times greater in diabetic than in non-diabetic persons between the ages of forty and fifty but only eighty-five times greater at ages fifty to sixty and fifty-three times greater at ages sixty to seventy.

TABLE I
INCIDENCE OF CORONARY OCCLUSION AT NECROPSY IN OLDER AND YOUNGER SUBJECTS WITH AND WITHOUT DIABETES*

	Per cent of Cases	
	Age under 40	Age 40 to 60
Diabetics	6	23
Non-diabetics	0.6	6

* From Root, Bland, Gordon and White.[44]

Concerning the vascular lesions that are more specific for diabetes, some studies indicate that intercapillary glomerulosclerosis occurs predominantly in the older ages.[14,52] No doubt this is true, for the older diabetics outnumber the younger, but there is a growing realization, as pointed out by Wilson, Root and Marble,[19] that the highest *incidence* of this form of renal disease is in patients in their thirties and forties with long-standing, poorly controlled diabetes. In Goodof's study[15] the frequency of the Kimmelstiel-Wilson lesion rose with age between ten and thirty years but then leveled off until age seventy when a rise occurred in both diabetics and non-diabetics. There was no appreciable difference in incidence between age thirty and ages sixty to seventy, suggesting that senescence does not increase susceptibility to this disorder. The same seems to be true for retinopathy.[28,47,54]

The dominant part played by long duration of diabetes has been thoroughly established.[3,4,6,15,20,28,51,55,56] The studies of White and Waskow[4] are most striking. Among 200 patients having onset before the age of fifteen and surviving for more than twenty years they found the following: "nephritis" in 50 per cent, calcified arteries in 75 per cent and retinal hemorrhages in 80 per cent. These consequences or concomitants of diabetes are uncommon in the early years of the disease but between the tenth and twentieth years of diabetes they assume alarming proportions. After twenty to twenty-five years increasing duration is less effective in augmenting the frequency of vascular lesions.[6,57]

The inter-relationship between duration of diabetes and age at death as they affect renal disease is brought out by Bell.[6] Table II, taken from his data, shows that for durations under ten years the incidence of intercapillary glomerulosclerosis increased from 3 per cent at ages twenty to forty to 20.3 per cent at ages sixty to ninety, whereas for durations over twenty years it decreased, oddly enough, from 100 per cent at ages twenty to forty to 41.4 per cent at ages sixty to ninety. Expressed in other terms, for short duration age increases frequency sevenfold, while for younger ages long duration increases frequency thirty-three fold. Bell's data[6] for renal arteriolosclerosis reveal similar trends, as do those of Root[20] for "nephritis." Here again it is evident that long-standing diabetes has its greatest effects in younger patients.

TABLE II
INCIDENCE OF INTERCAPILLARY GLOMERULOSCLEROSIS AT NECROPSY IN RELATION TO AGE AT DEATH AND DURATION OF DIABETES*

Age at Death (yr.)	Per cent of Cases		
	Duration Less than 10 yr.	Duration 10 to 20 yr.	Duration Over 20 yr.
20 to 40	3	51.4	100
40 to 60	19.8	41.7	65
60 to 90	20.3	36.5	41.4

* From Bell.[6]

Finally, despite what has just been said, long life with diabetes does not necessarily spell disaster. Bell[3] found that twenty-eight of ninety-three persons who lived more than twenty years after onset did not have serious vascular disease at necropsy. And although 92 per cent of White's[4] long-term patients had lesions of one sort or another, many of these were not severe and 8 per cent of the patients had none.

Severity of Diabetes. The statement is often made that severity of diabetes has no relation to the occurrence of vascular lesions.[6,14,24,28] This statement needs examination. How is severity determined? Usually it is judged by insulin requirement because this is the only way in which it can be expressed in numerical terms.

No one would deny that the diabetic patient who requires no insulin has the disease in mild form. It is even reasonable to suppose that in patients who do take insulin there is some rough, over-all correlation between severity and insulin dosage. But instances in which this correlation fails are fairly numerous and very important. The true test of severity is the behavior of the disease when insulin is withheld. There are many patients, chiefly those with onset of diabetes at a young age, who require doses of less than 40 units daily but in whom acidosis develops promptly when treatment is stopped. On the other hand, many patients with high requirements, principally in the older age groups, tolerate the withdrawal of insulin for days or weeks with no more than moderate glycosuria. Surely the former group represents the more severe degree of diabetes, and it is in these younger patients with long-standing disease that the incidence,[19] and one might add the seriousness, of vascular disease is most marked. The use of insulin requirement as an index of severity, and the preponderance in postmortem material of older subjects with mild diabetes but a considerable incidence of vascular lesions, due in part to aging, have no doubt contributed to the impression of pathologists that such lesions are as frequent in mild as in severe diabetes. Illuminating and indispensable as the observations of the pathologist are, it might be questioned whether he is in a position to evaluate severity as well as the clinician.

Although severity is probably more important in predisposing to vascular disease than has been generally realized, it must be granted that a good many patients with indisputably mild diabetes suffer from degenerative changes while others whose disease is obviously severe escape.

Control of Diabetes. The argument over the role of control is much like that over the role of severity, except that it is more heated, and the same kinds of questions present themselves. What is control? Are there more than a handful of "juvenile" diabetics who *can* be well controlled at all times? Is good control in severe diabetes the equivalent of poor control in mild diabetes? Can the pathologist, or anyone else for that matter, tell from a retrospective search of clinical records what the *habitual* degree of control has been in a patient who has seen his physician on only one day of thirty, ninety or 365 over a period of twenty years? The lack of satisfactory answers to these questions should be borne in mind in reviewing reports which attempt to relate degree of control of glycosuria to the occurrence of degenerative disease.

Perhaps it is well to start by reminding ourselves that in the few instances in which arterial and glomerular lesions have been observed in experimental diabetes, glycosuria has been relatively or entirely uncontrolled.[38–43] Similar experiments in which good control had been carefully maintained have not been described.

The notion that all diabetics, if they live long enough, eventually fall prey to vascular disease received strong support from the findings of Dolger in 1947.[54] In a group of 200 patients examined at frequent intervals for periods up to twenty-five years, none escaped retinopathy "regardless of age of onset, severity of diabetes or type of treatment used." Fifty per cent had hypertension and clinical evidence of renal disease at the time retinal hemorrhage first appeared. The group included fifty-five patients with onset of diabetes before the age of twenty. These fell into three subgroups of roughly equal size with glycosuria under excellent, fair and poor control, respectively. Retinopathy developed after ten to thirteen years in all the patients without relation to control, and there was little difference between the subgroups in the incidence of hypertension and no difference in arterial calcification. Albuminuria, however, occurred twice as frequently in those poorly controlled as in those very well controlled. No evidence that poor control favors or good control protects against vascular disease was found by Bell[3] for arteriosclerosis, Wagener, Dry and Wilder[53] for retinopathy, Henderson, Sprague and Wagener[14] for intercapillary glomerulosclerosis or Lundbaek[47] for all lesions except retinopathy.

Those who take the opposite view offer impressive evidence of a clinical nature. Among the 200 young patients of White and Waskow,[4] diabetic coma, certainly the epitome of poor control, had occurred in 17 per cent of those without degenerative lesions, in 38 per cent of those moderately affected and in 74 per cent of those incapacitated. A lower incidence of retinopathy in well controlled as opposed to poorly controlled patients was found by Spoont and his associates,[58] by Lundbaek[47] and by Jackson et al.,[59] the latter demonstrating also a smaller proportion of arterial calcification. Respecting "nephropathy," Root, Pote and Frehner[60] found the incidence of this condition among 451 patients with diabetes of ten to

thirty-four years' duration to be zero (eleven cases) for those with excellent control, 2 per cent (fifty cases) with good control, 17 per cent (ninety cases) with fair control and 28 per cent (298 cases) with poor control.

TABLE III
RETINOPATHY IN 189 PATIENTS WITH DIABETES OF TWENTY TO TWENTY-NINE YEARS' DURATION *

Degree of Control	Number of Cases	Per cent of Cases	
		No, or Slight, Retinopathy	Moderate, Marked or Extreme Retinopathy
Good	32	76	24
Fair	41	52	39
Poor	116	33	67

* From Root, Pote and Frehner.[60]

These authors carried out similar investigations of retinopathy. Table III, which summarizes their results, deserves special attention. It shows that of patients under good control retinopathy was absent or minimal in 76 per cent and moderate, marked or extreme in 24 per cent, while of those under poor control retinal lesions were absent or minimal in 33 per cent and moderate, marked or extreme in 67 per cent. Granted the difficulties, mentioned previously, of adequately evaluating control, it is probable that these workers have done it as well as is presently possible. Their data show clearly that a high incidence of severe retinopathy is associated with poor levels of control and a low incidence with good levels. However, they show just as clearly that one-fourth of the patients with good control had serious retinal damage and one-third with poor control had almost none despite very long-standing diabetes. These figures may be taken as representing fairly the relationship of control to the occurrence of vascular disease. They strongly suggest that the maintenance of a sugar-free urine will minimize the frequency and severity of vascular disease but that this alone is not sufficient in all cases. They suggest also that there is between individuals an inherent difference in the ability of the blood vessels to withstand insults of approximately equal degree and duration.

Adrenal and Pituitary Hormones. The capillary lesions of the retina and glomerulus, as has already been indicated, have much in common. Their concurrence, while not quite universal, is extremely frequent, aneurysmal dilatations have been described in both, and both apparently contain mucopolysaccharides as revealed by staining reactions. It is therefore natural to suspect that they have a similar pathogenesis. A number of recent observations have tended to implicate adrenocortical hormones or their pituitary trophic substances. Several cases have been reported[61–63] in which diabetic retinopathy first appeared or became much worse during pregnancy and in some instances subsided after delivery, suggesting that some disturbance of steroid metabolism may be involved. In 1952 Rich[64] described lesions resembling the Kimmelstiel-Wilson type in a non-diabetic subject who had received large doses of corticotropin for long periods of time. In that same year Becker,[63] working with Friedenwald, reported the appearance of similar renal lesions, as well as retinal microaneurysms, in alloxan-diabetic rabbits treated with corticotropin. Alloxan alone was ineffectual. These results have been confirmed in part by Bloodworth and Hamwi[65] who demonstrated both nodular and diffuse glomerular lesions in normal and alloxanized rabbits treated with cortisone. The lesions, however, tended to disappear after six weeks even though treatment was continued. These authors make no statement about retinopathy. Extending his investigations of the adrenal glands, Becker[66] has found that diabetic patients with retinopathy exhibit heavier adrenal weights with more cortical vacuolization, excrete more oxysteroids in the urine and more consistently show a normal eosinopenic response to corticotropin than do patients without retinopathy.

In 1953 Poulsen[67] reported the now famous case of a woman who had acquired diabetes in 1924 at the age of nine years. In 1945, at the age of thirty, diabetic retinopathy was found. In the same year a pregnancy, resulting in a stillborn fetus, was followed by severe uterine hemorrhage with the subsequent development of Sheehan's syndrome. By 1949 the retinopathy had diminished and by 1951 it had disappeared.

It is not surprising that the sum total of these observations has led to attempts to ameliorate diabetic vascular disease by removal of the pituitary and adrenal glands. A series of hypophysectomies reported in 1953 by Luft and Olivecrona[68] included four cases of juvenile diabetes, three with advanced vascular disease.

Postoperative survival was brief in three patients, however, and no significant data respecting vascular disease are available in the fourth. In 1954 Kinsell and his co-workers[69] published an account of four patients with diabetes in whom hypophysectomy had been performed for severe renal and retinal disease. A number of interesting and expected metabolic results ensued but even one year later, after eighteen months' observation in some cases, the authors were unable to say that any unequivocal, permanent improvement in vascular status had taken place.[70] Also in 1954, Wortham and Headstream[71] reported on bilateral adrenalectomy in seven similar cases. Of these, two are said to have shown minor reversals of retinal changes and diminished blood pressure, proteinuria, azotemia and edema; in three cases the process was considered arrested; and two patients experienced progressive renal failure terminating in death from vascular accidents. Taken together, the results of these surgical procedures are not impressive as of this date.

It might be expected that examination of the retina in patients with either acromegaly or Cushing's syndrome and diabetes would be revealing. Only two such studies are available. Of twenty-one patients with acromegaly and diabetes, McCullagh and Alivisatos[74] found diabetic retinopathy in three after eight, five and two years of known diabetes, respectively; and of twenty-one patients with Cushing's syndrome and diabetes, diabetic retinopathy appeared in two after nine and eight years of known diabetes, respectively. Ricketts[75] found diabetic retinopathy in two of three patients with acromegaly and diabetes, and in none of seven patients with Cushing's syndrome and diabetes. Thus diabetic retinal disease is apparently infrequent in combination with hyperactivity of either the anterior pituitary or adrenal cortex, although it has occurred unusually early in the course of diabetes in some of the patients who showed it. Comparable investigations of hypopituitarism, with the exception of Poulsen's,[67] and of Addison's disease do not seem to have been published.

It is of the greatest importance that a method of experimentally producing capillary lesions resembling those of human diabetes has finally been discovered. It is still quite uncertain, however, to what degree, if any, adrenocortical substances are responsible for these lesions in man. The evidence adduced by Becker[66] is at this point only suggestive. The results of determinations of urinary steroids in diabetes are conflicting,[66,72,73] and there certainly is no reason to believe on clinical grounds that the long-term diabetic patient is suffering from adrenal hyperactivity. It may be that the role of the adrenal is a permissive one, merely allowing the development of lesions whose primary etiology lies in other areas.

BIOCHEMICAL FACTORS

Aside from any consideration of endocrine influences, the fact that the incidence and degree of vascular lesions are clearly related to the duration of diabetes, and probably to its severity and control, suggests that there may be some associated biochemical abnormality which, acting over long periods of time and with considerable intensity, favors, if it does not determine, the development of such lesions. The obvious abnormalities are hyperglycemia and hyperlipemia.

Hyperglycemia. No one has ever seriously proposed that concentrations of blood sugar, such as prevail in long-term diabetes, are in themselves injurious to intimal tissue, although it has been postulated without proof that extreme fluctuations may be harmful. It is possible, however, that some factor related to hyperglycemia may be implicated. In this connection attention has been directed to the mucopolysaccharides because of their presence in both retinal microaneurysms and the glomerular lesions of Kimmelstiel and Wilson. Earlier work in diabetic patients which indicated a direct relationship between levels of blood glucose and glucosamine,[76] a component of mucopolysaccharides, has not been conclusive.[77] Berkman and others[77] nevertheless demonstrated higher levels of protein-bound polysaccharides and glucosamine in the serum of patients with clinically apparent vascular disease than in those without. Nielsen and Poulsen[78] found increased concentrations of similar compounds in the blood of diabetic patients without complications as well as in those with renal disease. These results were confirmed by Keiding and Tuller[79] who found in addition that levels in patients with "nephropathy" were higher than in those showing degenerative lesions without nephropathy. Gilliland et al.[80] report some parallelism between polysaccharide levels and the degree of vascular disease but also some increase in levels before such disease was clinically manifest. Investigations of the urinary excretion of these substances

have shown no correlation with diabetes or its complications.[81] In view of the increased concentrations of serum mucopolysaccharides that are known to occur in conditions characterized by tissue destruction and repair,[77] it is possible that the higher values observed in diabetes may be the result of degenerative disease, either patent or occult, rather than its cause. Regardless of such cautionary considerations, the subject deserves the further study that it is certain to receive.

*Hyperlipemia.** Except for the presence of fat in a considerable proportion of the lesions of intercapillary glomerulosclerosis,[11] there is little reason to believe that hyperlipemia has any etiologic significance for that condition or for diabetic retinopathy. Its relationship to atherosclerosis in general has been the subject of a vast body of literature. The tendency of diabetic individuals toward both abnormal fat metabolism and atherosclerosis has often been used as an argument favoring a causal relationship between the two even in non-diabetic persons. It is pertinent to inquire, however, as to the frequency of high levels of serum lipids in the ordinary diabetic patient. "For our present purposes, we are not interested in the characteristic lipemia of the untreated diabetic or of the diabetic in acidosis. If the lipids have any significance for vascular disease, it must be by virtue of the levels which prevail in the treated diabetic over a long period of years. The literature contains surprisingly few reports on this subject, and those that we have are not only conflicting but are based on analyses made at only a single point in time.†

"Chaikoff and others[83] compared serum cholesterol, phospholipids and fatty acids in twenty-three normal children and twenty-six children with diabetes under good control with diet and insulin. They found no appreciable difference between the two groups, nor did the duration of diabetes or the daily insulin requirement (10 to 68 units) have any relation to the cholesterol levels. Man and Peters[84] found the serum cholesterol normal or below in 64 per cent of seventy-nine diabetics not suffering from dehydration or acidosis. Of nineteen patients who showed rather marked hypercholesterolemia, sixteen had complicating conditions such as cirrhosis or nephritis which in themselves might have explained the high cholesterol levels. Among the uncomplicated cases the cholesterol did not exceed 304 mg. per cent—certainly not a striking figure. Pomeranze and Kunkel[85] recently examined two hundred seventy-three diabetics in various clinics in New York City. Almost exactly half had total lipids above 750 mg. per cent (the upper limit of normal) while the other half had levels below this." Among 614 diabetic patients, Barach and Lowy[86] found 42 per cent with normal and 58 per cent with high cholesterol values. Lundbaek[47] found the average serum cholesterol concentration in 151 long-term patients to be only 256 mg. per 100 ml. In patients below the age of forty, values were from 30 to 40 mg. higher in diabetic than in normal persons, but above the age of forty there was no significant difference.

"These data suggest that in children with well controlled diabetes there is little if any increase in blood lipids but that among adults, with diabetes of varying severity and under varying degrees of control, the lipids are elevated, although not markedly so, in 35 to 58 per cent of the cases.

"Respecting lipoproteins in diabetes, Barach and Lowy[86] report the Sf 12–20 fraction above 50 mg. per cent in 33 per cent of males and 43 per cent of females. Hanig and Lauffer[87] were unable to find any significant difference between normal persons and diabetics. The data of Keiding and associates[88] would justify a similar conclusion, although they do not state it in so many words. Among the diabetics themselves, Sf 12–20 levels tended to be higher in patients under poor control than in those under good control.

"The next question is whether the diabetics who do have hyperlipemia are the ones who also have vascular disease. Among the cases studied by the New York group,[85] 78 per cent of the patients with hyperlipemia had severe atherosclerosis as shown by electrocardiographic evidence of coronary disease, calcified vessels or retinal arteriosclerosis. Twenty-two per cent were classed as having moderate atherosclerosis or none. On the other hand, of the patients who had normal serum lipids about 40 per cent had severe atherosclerosis and 60 per cent had a moderate amount or none. We are left, then, with the dilemma of what caused the vascular disease in the 40 per cent without hyperlipemia.

"Referring again to the lipoproteins, Barach[86]

* The ensuing passages indicated by quotation marks are taken from an earlier review of this subject by the author.[82]

† See footnote, page 942.

found the Sf 12–20 fraction elevated in 45 per cent of one hundred sixty-two diabetics with vascular calcification. This is not significantly different from the incidence of elevated Sf 12–20 levels in the entire group of diabetics. Essentially the same results were reported by Keiding,[88] with the additional surprising finding that lipoproteins were distinctly increased in patients with retinopathy. It is not stated how many of the patients with retinopathy also had the Kimmelstiel-Wilson lesion—a condition in which the Sf 12–20 levels are almost uniformly high."[89]

Finally, studies of quite a different sort by Hirsch and his colleagues[90] have shown that in diabetic persons the esterified fatty acids of the blood, in contrast to cholesterol and lipoproteins, rise abruptly after a fat meal and that the increase is greater during periods of hyperglycemia than during normoglycemic periods. The fasting levels, moreover, when determined day after day in patients with unstable diabetes, rise and fall *pari passu* with the fasting blood glucose. If it were established that arterial disease is in fact induced by hyperlipemia, these observations would provide a powerful argument for strict control of the blood sugar.

To summarize, hyperlipemia is not a prominent feature of treated diabetes. It is present to a greater extent in patients with poorly controlled than in those with well controlled glycosuria. Studies of its relation to vascular disease have yielded inconsistent results. Respecting atherosclerosis, there are no available data on serial determinations of serum lipids in the same diabetic patients over a period of years.* Single analyses suggest some association between elevated lipid concentrations and the presence of atherosclerosis, but such association is lacking in a large number of cases. Even a good correlation would not prove a cause and effect relationship. Patients with presumed intercapillary glomerulosclerosis have higher lipid levels than those without, but lipids are also elevated in non-diabetic persons with other forms of nephritis. It is probable that the hyperlipemia of some patients with retinopathy is explained by the presence of renal disease.

* In a study of intercapillary glomerulosclerosis, in which data for atherosclerosis are not given, Mann, Gardner and Root[91] report that in patients for whom information on cholesterol was available, values were normal when the patients first came under treatment and remained so for the first ten years of diabetes, rising to abnormal levels only with the onset of symptoms of nephritis.

SUMMARY

Diabetes, or some factor related to it, markedly hastens the onset and increases the frequency and severity of arterial and arteriolar sclerosis. In addition, it gives rise to capillary lesions of the renal glomeruli and retina that belong almost exclusively to the diabetic state. Rates of death and disability from these causes are increasing as diabetic patients live longer.

Diabetes increases susceptibility to atherosclerosis to a greater extent in women than in men, and the former have a higher incidence of intercapillary glomerulosclerosis but not of retinopathy.

Although instances of vascular disease are observed in greater numbers among older patients, its incidence and seriousness in younger patients with long-standing diabetes are striking. Duration of diabetes stands out as the most important single factor, and its effects are greater in younger than in older persons.

The parts played by severity and control of diabetes are still in dispute. The best evidence indicates that the highest frequency of advanced lesions occurs in severely diabetic patients with prolonged, heavy glycosuria. It is clear, however, that some patients with mild, well controlled diabetes have manifest vascular lesions while their opposite numbers seem to escape. These inconsistencies lend support to the concept, as yet incapable of proof, that hereditary tendencies may be as important as diabetes itself.

The experimental production of both glomerular and retinal lesions with cortisone and corticotropin strengthens the possibility that they have a common pathogenesis in man and raises the question of whether their clinical occurrence is related to adrenal hyperactivity. Evidence on this point is contradictory.

Mucopolysaccharides are increased in the blood of diabetic patients with vascular, especially renal, disease but to some extent in those without it and may be related to the pathogenesis of retinopathy and intercapillary glomerulosclerosis.

Hyperlipemia in the treated diabetic patient is neither so frequent nor so marked as has been commonly supposed. To the extent that it does exist its association with atherosclerosis is loose and inconstant and in many cases is lacking entirely. Elevated lipid levels in intercapillary glomerulosclerosis are probably a result rather than a cause of the disease.

The etiology and pathogenesis of diabetic vascular disease remain obscure.

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Clinico-pathologic Conference

Hypertension, Abdominal Pain and Nausea, Syncope and Shock

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

PATIENT H. H., (History No. 230473), a forty-six year old white married housewife, was admitted to the Barnes Hospital for the first time on December 20, 1953, with a chief complaint of "blackout spells" two hours prior to admission.

The patient was said to have had hypertension during both of her pregnancies. However, blood pressure returned to normal between pregnancies. Two years prior to admission she had a hysterectomy, appendectomy and oophorectomy because of persistent metrorrhagia. At that time she was found to have sustained hypertension and cardiac enlargement. Following this operation she had repeated episodes of hot flashes for which she was given oral hormones intermittently without relief. She had occasional headaches and episodes of epistaxis. About six to eight weeks prior to admission she began to have attacks of irregular beating of her heart and an uncomfortable feeling of fullness in her head, "like everything was rushing into my head." She would feel as if she were going to faint but never did. She also noted ringing in her ears and occasionally an unsteady feeling. On the day prior to admission she had such an episode which passed off without sequelae. Because of her palpitation and the finding by her attending physician several weeks prior to admission of ventricular premature contractions, she was placed on quinidine, 0.2 gm. four times a day, which did not seem to affect the frequency of occurrence of her palpitations. A blood pressure reading in her physician's office several weeks prior to admission was in the range of 240 to 250/110 to 120.

Two hours prior to admission, while lying down, a feeling of fullness in her head developed and she became unconscious. There were no other premonitory symptoms. She did not convulse, bite her tongue or injure herself and there was no incontinence of urine or feces. She did, however, stop breathing and a neighbor began to breathe into her mouth. Police were called and an inhalator was used. Her attending physician arrived approximately thirty-five minutes after the onset of her unconsciousness. He found her in "pulmonary edema" with a very weak pulse. She was given 150 mg. of aminophylline intravenously. Prior to this episode the patient had never had any symptoms of cardiac decompensation such as orthopnea, paroxysmal nocturnal dyspnea, dependent edema, or dyspnea on slight to moderate exertion.

Her past history was notable in that eight years prior to admission she had episodes of nausea without pain and was said to have had a peptic ulcer which was treated with a bland diet, pills, and non-absorbable antacids, following which her symptoms subsided. Several months prior to admission she had an episode of epigastric tightness and distress, most marked in the right upper quadrant. Roentgen examinations of the gastrointestinal tract, gallbladder and kidneys were said to be negative. She was told several months prior to admission that her episode of abdominal distress was probably a recurrence of her ulcer, and she was advised to follow a bland diet again. One stool was found to contain blood but she had never noted gross blood or melena although she had looked for it. There was no jaundice.

The family history disclosed that her mother died at the age of seventy and her father at the age of sixty-nine, both of strokes.

Physical examination at the time of admission revealed the patient's temperature to be 37.1°C.;

pulse, 100; respirations, 16 and blood pressure, 150/100. The patient was apprehensive, slightly cyanotic and confused. She was well developed, well nourished, acutely ill and coughing frequently. There was no lymphadenopathy. Examination of the eyes revealed normal extraocular movements. The pupils were round and equal and reacted to light. Examination of the fundi revealed slight arteriolar-venous nicking without papilledema, hemorrhages or exudates. On the right posterior oral pharyngeal wall were yellow punctate lesions, each of which was surrounded by an area of erythema. Her neck was supple and the thyroid was not palpable. There were a few fine rales at the left lung base. The heart was enlarged to the anterior axillary line with a well localized point of maximum impulse in the fifth intercostal space. There was a harsh, grade II systolic murmur best heard in the region of the pulmonic area. There was a regular diastolic gallop rhythm at the apex. The sounds were of poor quality. No masses or organs were palpable on abdominal examination. Examination of the extremities revealed slight cyanosis of the nail beds. There was no edema or clubbing. Pedal pulses were present. The remainder of the physical examination, including the neurologic examination, was not remarkable.

The laboratory data were as follows: red blood cell count, 6,320,000 per cu. mm.; hemoglobin, 16.8 gm. per cent; white blood cell count, 21,050; differential count: stab forms, 3 per cent; segmented forms, 75 per cent; lymphocytes, 19 per cent; monocytes, 3 per cent. Urinalysis: specific gravity, 1.008; pH, 7.0; protein, 2+. Serologic test for syphilis: negative. Sputum culture: moderately heavy growth of neisseria, slight growth of staphylococci and alpha hemolytic streptococci. Electrocardiogram: left ventricular strain, question of subendocardial myocardial injury, sinus tachycardia and quinidine effect. Blood chemistry: non-protein nitrogen, 22 mg. per cent; fasting sugar, 106 mg. per cent; two-hour postprandial sugar, 96 mg. per cent; carbon dioxide combining power, 31 mM/L.; prothrombin level, 80 per cent of normal. Erythrocyte sedimentation rate, 4 mm. per hour, corrected.

The patient was given oxygen by nasal catheter, following which there was an immediate disappearance of cyanosis and an increase in alertness; nasal oxygen was continued for four days. An electrocardiogram on the second hospital day showed no change from the one taken on the first. Venous pressure on the second hospital day was 45 mm. of water; arm-to-tongue circulation time was twenty-two seconds. On the third hospital day the patient's lungs were clear to auscultation. An electrocardiogram on the fourth hospital day showed T wave inversion across the precordium compatible with anterior myocardial ischemia or pericarditis; subendocardial myocardial injury was no longer evident, and there was less evidence of quinidine effect. A repeat blood count on the fourth hospital day was as follows: red blood cell count, 4,690,000; hemoglobin, 13.5 gm. per cent; white blood cell count, 9,300; differential count: eosinophils, 2; stab form, 1; segmented forms, 56; lymphocytes, 40; monocyte, 1. Red blood cells showed slight hypochromasia. On the fifth hospital day a pericardial friction rub was heard in the second and third left intercostal spaces along the left sternal border. This rub persisted to the fifteenth hospital day. During this time the patient's lungs were otherwise clear on physical examination. The systolic gallop rhythm heard at the apex of the heart persisted. An electrocardiogram on the eleventh hospital day was interpreted as showing reappearance of subendocardial myocardial injury, left ventricular strain and sinus tachycardia. Subsequent electrocardiograms revealed resolving subendocardial myocardial injury, then left ventricular strain with a question of anterior myocardial injury, then left ventricular strain with a question of anterior myocardial ischemia, and finally only an abnormal form of ventricular complex on the fifty-ninth hospital day. Quinidine in doses of 0.2 gm. four times a day and later three times a day was continued throughout her hospitalization.

During the first week of the patient's hospital course her blood pressure ranged from a high of 180/120 to a low of 130/90. On the third hospital day apresoline® in doses of 25 mg. three times a day was started. This dose was gradually increased and on the eleventh hospital day hexamethonium chloride was administered. The patient's blood pressure continued to fluctuate considerably until approximately the last two weeks of hospitalization when her blood pressure stabilized in the approximate range of 160 to 170/90 to 100. The patient remained on absolute bed rest until the twenty-eighth hospital day when gradually increasing ambulation was begun. Repeated determinations of the blood

non-protein nitrogen were within normal limits. The erythrocyte sedimentation rate was normal until the thirty-second hospital day when it was 23 mm. per hour; on the forty-second hospital day it was 28 mm. per hour. On the fifty-second hospital day the phenolsulfonphthalein excretion was 24 per cent in fifteen minutes and 67 per cent in two hours. Urine concentration test at eighteen hours produced a specific gravity of 1.012. The patient tolerated her medication quite well and was discharged on February 18, 1954, on doses of apresoline, 100 mg. every four hours (except at 2 A.M. when the dose was to be omitted) and hexamethonium every four hours, the dose not to exceed 200 mg. every four hours according to the blood pressure which was to be determined by her husband. She was also given a sedative and a non-absorbable antacid.

The patient continued her antihypertensive therapy and had no untoward complaints until one week prior to her second admission when she first noted epigastric "fullness and tightness" and a "cold" which she treated with aspirin, bicarbonate of soda and a bland diet. She had no fever or sore throat. She was admitted on September 24, 1954.

Physical examination on this admission recorded the patient's temperature to be 36.6°C.; pulse, 88; respirations, 18 and blood pressure 180/120. She appeared chronically ill and complained of abdominal discomfort. Examination of the abdomen revealed diffuse tenderness most marked in the mid-epigastrium without muscle guarding, rigidity or rebound tenderness. Bowel sounds were normal. In the right upper quadrant there was felt to be a tender cystic mass which moved with respirations. The remainder of the physical examination was otherwise as on her previous admission.

The laboratory data were as follows: hemoglobin, 14.0 gm. per cent; white blood cell count, 12,650; differential count: segmented forms, 69 per cent; lymphocytes, 28 per cent; monocytes, 3 per cent. Urinalysis: specific gravity, 1.017; pH, 7.5; protein, 1+; sugar, negative; microscopic examination: two to four white blood cells per high power field. Stool examination: guaiac-negative. Blood chemistry: non-protein nitrogen, 30 mg. per cent; fasting sugar, 71 mg. per cent; cholesterol, 262 mg. per cent; albumin, 4.3 gm. per cent; globulin, 2.7 gm. per cent; alkaline phosphatase, 8.1 Bodansky units; total bilirubin, less than 0.8 gm. per cent; icterus index, 21.7 units; cephalin cholesterol flocculation, negative; thymol turbidity, 0.9 units. An electrocardiogram on admission showed a full auriculoventricular conduction time but was otherwise within normal limits. Roentgen examination of the chest revealed bilateral upper lobe fibrocalcific tuberculosis. Routine cholecystograms revealed cholelithiasis; the gallbladder was well visualized.

The patient vomited food and liquids on several occasions but her symptoms gradually subsided. It was felt on subsequent examinations that the "mass" in the right upper quadrant was only rectus muscle. Blood chemical determinations done on the fourth hospital day were as follows: alkaline phosphatase, 3.2 Bodansky units; amylase, 200 units; prothrombin level, 80 per cent of normal. Her blood pressure was within normal limits through most of her hospital stay with only an occasional rise to hypertensive levels. She was discharged asymptomatic on the seventh hospital day, September 30, 1954.

The patient had apparently continued her antihypertensive therapy, varying the dose according to the blood pressure. She took only 125 mg. of hexamethonium chloride on the day prior to admission; she had taken none on the day of admission. About 6:30 A.M. on October 11, 1954, she began to have generalized cramping abdominal pain, most marked in the suprapubic area, associated with vomiting on one occasion and gagging. The cramping was also associated with the desire to defecate but she was unable to do so. She gave herself a small enema without recovery of the enema fluid. There had been no bowel movement on the day prior to admission. However, there was a normal bowel movement the day before that. The cramping continued intermittently all during the day of admission.

On this admission the patient's temperature was 37.5°C.; pulse, 104; respirations, 22 and blood pressure 120/80. The patient appeared chronically ill and preferred to have her knees and legs flexed while lying on her side. On abdominal examination a mass thought to be the sigmoid colon full of feces was felt in the left lower quadrant. In the right lower quadrant there was tenderness without rebound. Bowel sounds were hypoactive. There was no hyperperistalsis associated with cramping. The remainder of the physical findings had not changed from the last examination on the previous admission.

The laboratory data were as follows: hemoglobin, 16.8 gm. per cent; white blood cell count, 22,525; differential count, stab forms, 12 per cent; segmented forms, 80 per cent; lymphocytes, 7 per cent; monocytes, 1 per cent. Urinalysis: specific gravity, 1.010; pH, 7.4; protein, negative; sugar, negative; microscopic examination: occasional hyalin cast, occasional epithelial cell, few phosphate crystals; bilirubin, negative. Stool: guaiac-negative. Urine culture: few colonies of coagulase-negative Staphylococcus albus. Blood chemistry: non-protein nitrogen 33 mg. per cent; fasting sugar, 131 mg. per cent; amylase, 89 units; cephalin cholesterol flocculation, negative; thymol turbidity, 1.5 units; total serum bilirubin, less than 0.8 mg. per cent; albumin, 5.2 gm. per cent; globulin, 3 gm. per cent; alkaline phosphatase, 8.4 Bodansky units; calcium, 11.3 mg. per cent; phosphorus, 5.9 mg. per cent; sodium, 137.9 mEq./L.; potassium, 3 mEq./L.; chloride, 94 mEq./L.; carbon dioxide combining power, 20.8 mM/L. An L.E. cell preparation was negative. Blood culture: no growth. An electrocardiogram was interpreted as follows: "The marked positional changes with the tall R wave in AVR point strongly toward a pulmonary embolus." Posterolateral myocardial infarction, indeterminate heart position with marked clockwise rotation and sinus tachycardia were also diagnosed.

The patient's blood pressure after admission was extremely labile, reaching a height of 220/140 three hours after admission, but early on the morning of the second hospital day it began to fall. Concomitant with the fall in blood pressure her temperature began to rise. Ten milligrams of vasoxyl® given intramuscularly produced only a transient rise in her blood pressure with a prompt return to a level in the range of 70 systolic, the diastolic pressure being unobtainable. The patient continued to have abdominal pain and vomited guaiac-positive material. She was given intravenous fluids to which nor-epinephrine was added on the morning of the second hospital day. Her blood pressure responded only transiently. Her level of consciousness decreased progressively; on the morning of her second hospital day she became totally unconscious. Despite the addition of increasing amounts of nor-epinephrine to the intravenous fluids, her blood pressure continued to fall. Her temperature increased to 42.5°c. She was placed in a refrigerated oxygen tent and icebags were placed on her abdomen and axillas. Her respirations became increasingly more gasping and on the morning of her second hospital day they ceased entirely, her heart sounds could not be heard and her blood pressure was unobtainable. An intracardiac injection of 1 cc. of 1:1000 epinephrine failed to produce a response. Blood chemical determinations obtained prior to her death on the second hospital day were as follows: non-protein nitrogen, 60 mg. per cent; chloride, 90 mEq./L.; carbon dioxide combining power, 15.6 mM/L. She died on October 12, 1954.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: We should perhaps first consider what type of hypertension this patient had. She was said to have had hypertension during her two pregnancies, with a return to normal blood pressure between pregnancies. There was no information in the chart as to how long ago either of these pregnancies occurred. In 1951, two years prior to her first admission to the Barnes Hospital, she was found to have sustained hypertension when she was hospitalized for hysterectomy. Following this operation she had occasional headaches and episodes of epistaxis. From that time until twenty-four hours before her death she had a variable but definite hypertension. Several months prior to her first admission intravenous pyelograms were taken elsewhere and were said to have been normal. During her first admission to the Barnes Hospital she had 2+ proteinuria on one occasion; forty-eight hours later there was no proteinuria. Her blood nonprotein nitrogen concentration was normal then, and remained so until she went into shock twenty-four hours before her death. The history at the time of her first admission stated that the patient had been emotionally very unstable and subject to anxiety attacks since her hysterectomy; these were more severe after her mother died of a cerebral hemorrhage in February, 1953. We have no information about the patient's emotional status prior to the onset of her hypertension. Both the patient's mother and father are stated to have died of strokes. Dr. Schroeder, do you think the hypertension we are dealing with here is essential hypertension? That was the clinical diagnosis. Do you see any reason to doubt it?

DR. HENRY A. SCHROEDER: I never make a diagnosis of essential hypertension. It is very

hard to tell from the protocol just what kind she had. I would suspect that she had what we might call neurogenic hypertension, associated with overactivity of the autonomic nervous system, or she may even have had an endocrine component. She had had a hysterectomy and had hypertension with her pregnancies; it is possible that she may have had adrenal hyperplasia or even a small adenoma.

DR. REINHARD: Does anybody have anything to add to this? We can agree with Dr. Schroeder that the data available do not permit us to define the hypertension much more precisely.

DR. EDWARD MASSIE: Dr. Reinhard, I would like to ask Dr. Schroeder if this patient could have had a pheochromocytoma? She was young, she had arrhythmias, abdominal pain and many other features described in patients with that disease; perhaps we have information about her only at the stage of her disease when the blood pressure was persistently elevated.

DR. SCHROEDER: That is a very good suggestion, Dr. Massie. The history of hot flashes and palpitation could be consistent with either neurogenic hypertension or with pheochromocytoma. I suspect that when one gives a ganglionic blocking agent to a patient with pheochromocytoma the blood pressure does not come down. As a matter of fact, these drugs may make the tumor discharge. I have not had that experience myself but it has been reported.

DR. REINHARD: In view of the fact that no tests were performed to make the diagnosis of pheochromocytoma, I believe we can only say that this is a possibility here. Let us consider the blackout spells which were the immediate cause of this patient's first admission. Six to eight weeks prior to admission she began to have attacks of irregular beating of her heart, an uncomfortable feeling of fullness in her head, a ringing in her ears, and a feeling that she was going to faint although she never did. One day prior to admission she had an episode of this sort which passed off without any sequelae. Because of her palpitation and the finding by her attending physician several weeks prior to admission of ventricular premature contractions, she was placed on quinidine, .2 gm. four times a day; this did not seem to affect the frequency or severity of the palpitations. Blood pressure readings in her physician's office several weeks prior to admission were 240 or 250 systolic and 110 or 120 diastolic on several examinations. Two hours prior to admission, while she was lying quietly on a divan, a feeling of fullness in her head developed and she became unconscious. She did not convulse, did not bite her tongue and did not injure herself. There was no incontinence of urine or feces. She did, however, stop breathing, and a neighbor began to breathe into her mouth. Police were called and an inhalator was used. Her attending physician arrived approximately thirty-five minutes after the onset of her unconsciousness. He found the patient to be in pulmonary edema with a very weak pulse. She was given 150 mg. of aminophylline intravenously. Prior to this episode she had never had any symptoms of cardiac decompensation. The house officers who admitted this patient to the hospital thought this attack of unconsciousness was due either to a sudden cardiac arrhythmia or to decreased cerebral blood flow due to the cardiac decompensation. However, although the heart was enlarged, the liver was not; there was no edema and there was no very convincing evidence of cardiac decompensation. Dr. Massie, I believe you have studied this patient's electrocardiograms. Would you tell us what the electrocardiograms on this admission showed, and then explain to us what you think these attacks of palpitation, as well as the single episode of unconsciousness, might have been due to. Were these due to the same cause or to different causes?

DR. MASSIE: Looking over the eleven electrocardiograms I would say this patient suffered successively myocardial ischemia, left ventricular strain, myocardial injury and then subsequently developed a fairly normal record. In the first set of tracings ischemia is seen primarily, and I can go no further than to blame coronary insufficiency as the cause of the electrocardiographic findings. I would not necessarily incriminate the heart as the cause of the blackout spell.

DR. REINHARD: This patient did have a pericardial friction rub from the fifth to the fifteenth hospital day. How do you account for this?

DR. MASSIE: I do not believe that this patient had a myocardial infarction. Therefore, I would not make a diagnosis of pericarditis resulting from myocardial injury and infarction. I cannot explain why she had pericarditis; the electrocardiogram is not very impressive, and I wonder whether she did have it. The friction rub may have been something else. I presume it was not a pleural–pericardial friction rub?

DR. REINHARD: Dr. Wilson, was this a friction rub?

DR. KEITH WILSON: I thought it was a pericardial friction rub.

DR. MASSIE: In that case, I cannot explain it on the basis of what I see in the protocol or the electrocardiogram. We would have to ascribe it to an arrhythmia. In these eleven electrocardiograms we have no arrhythmia. I do not know how cerebral syncope occurs in cardiac disease without shock, without acute infarctions or without arrhythmias.

DR. REINHARD: Dr. Wilson, did this patient ever have an arrhythmia when you saw her in the office?

DR. WILSON: No, but I saw her only about two weeks before she entered the hospital.

DR. JOHN SMITH: The remark she made that there was a feeling of fullness in her head "like everything was rushing into my head" is extremely reminiscent of venous congestion, and one wonders whether or not these were episodes of sudden vasodilatation which were occasioned by some type of vagal depressor response. One wonders whether the carotid sinus might have been active in a patient like this, there being particularly a cerebral type of response; the palpitation therefore would follow in natural sequence to it.

DR. REINHARD: We may be comforted by the thought that there may be no pathologic changes to account for this attack of unconsciousness, but perhaps we will not have to apologize for that. We certainly cannot explain this adequately. Let us proceed now to the patient's second hospital admission seven months later in September, 1954. The chief complaint that brought the patient to the hospital this time was epigastric fullness and a tightness of the epigastrium, without any real pain, of one week's duration. The patient also had a cold. She apparently had been nauseous and had vomited several times during the two days before admission. Eight or nine years prior to this, at the age of thirty-eight, the patient had several episodes of nausea without pain. Apparently no x-rays were taken at that time, but she was told that she had a peptic ulcer and was treated with antacids and a diet following which her symptoms subsided. In the fall of 1954 she had episodes of epigastric tightness and right upper quadrant distress at which time gastrointestinal x-rays were obtained elsewhere; these were said to have been normal. We have not seen them. However, she was told that she probably had a recurrence of her ulcer and was put on a bland diet. She never had gross blood in her stools or melena, but one stool was-guaiac positive at the time of her second admission to the hospital or just before it. An electrocardiogram taken on the day of admission to the hospital showed prolonged conduction but was otherwise not remarkable. Six stool specimens examined while the patient was in the hospital were all guaiac-negative. I think the protocol mentions only one. This is a good time to see the x-rays, as no films were taken of this patient except during the second hospital admission.

DR. WILLIAM B. SEAMAN: On the first day of the second hospital admission the patient had examinations of the chest and abdomen. The examination of the chest showed a cardiac shadow that lay within the upper limits of normal. It might perhaps have been slightly enlarged, but without previous films it was impossible to say. She had calcified peritracheal nodes, a small focal parenchymal calcification lying in the subpleural position in the apex of the lower lobe, and in both upper lobes there were small focal areas of calcification. These all were compatible with an old calcified tuberculosis. The lungs were otherwise clear. The examination of the abdomen revealed a gas pattern in the intestinal tract which was not remarkable. The liver shadow extended down a little below the iliac crest; there was no evidence of calcified gallstones. There were a few calcifications overlying the kidney on the right side, but in the lateral view they seemed to lie within the substance of the liver rather than in the kidneys. Kidney shadows were normal in size. Three days later a cholecystogram showed normal visualization of the gallbladder, but overlying its shadow were some radiolucent areas which could have been stones.

DR. REINHARD: Dr. Wilson, this was your patient. Did you think the symptoms at the time of her second admission to the hospital were due to cholelithiasis or cholecystitis? That was the favorite clinical diagnosis while the patient was in the hospital. You will recall that the patient had an icterus index of 21 on the day of admission to the hospital, which in the presence of gallstones would certainly suggest common duct obstruction; however, the patient was not clinically jaundiced, and the total serum bilirubin on the same day was less than 0.8 mg. per cent, so one would suspect the icterus index

was due to some other factor. What was your impression at this time?

DR. WILSON: I did not see her at that time, but apparently everyone thought she had some process going on in her abdomen, most likely in the gallbladder.

DR. REINHARD: Dr. Mendeloff, would you like to make any comments about the probable cause of this patient's symptoms at this time?

DR. ALBERT I. MENDELOFF: None of the data we have, Dr. Reinhard, would allow me to state that her symptoms were due to gallstones, if she had them, or to an ulcer.

DR. REINHARD: The alkaline phosphatase was elevated at the time of her admission to the hospital, and four days later it was back to normal; however, during the patient's terminal hospital admission the alkaline phosphatase was again elevated. Would you like to comment on possible causes for the elevated alkaline phosphatase, Dr. Shank? Is it the result of liver disease?

DR. ROBERT E. SHANK: There is really no evidence of any liver disturbance in the protocol.

DR. REINHARD: Dr. Mendeloff, how about the amylase of 200 Somogyi units on the fourth day of this hospital admission? Is this of any help?

DR. MENDELOFF: An isolated amylase value of 200 is not really abnormal. There was a later value of 89. These were the only two that were recorded on this patient, and together they do not help us very much. We do know that people with hypertension have marked changes in their pancreatic vessels, and a number of them have a certain amount of pancreatitis which is not clinically significant. This woman did have some findings which suggest that she might have had pancreato-biliary disease, and she was hypertensive, but there was little to make me believe that she had an acute pancreatitis.

DR. REINHARD: The patient died twenty-two hours after the third and final hospital admission. She had apparently continued her antihypertensive therapy, varying the dose according to the blood pressure. She took only 125 mg. of hexamethonium chloride on the day prior to admission and had taken none on the morning of admission. At about 6:30 A.M. on the day of admission she began to have generalized cramping abdominal pain most marked in the suprapubic area but involving other areas as well. This was associated with vomiting on one occasion and considerable gagging. The cramping was also associated with the desire to defecate, but the patient was unable to move her bowels. She gave herself a small enema without recovering the enema fluid. There had been no bowel movement on the day prior to admission, but there was a normal movement the day prior to that. The cramping abdominal pain continued intermittently all during the day of admission to the hospital. The significant physical findings on admission were a temperature of 37.6°C. which rose rapidly thereafter. The blood pressure fluctuated widely for four or five hours from extreme hypertensive levels to almost normal or hypotensive levels, following which she went into shock and the blood pressure went down to shock levels and stayed there in spite of therapy. The abdominal pain was less severe when the patient lay on her side with her legs flexed. There was right lower quadrant tenderness without any rebound tenderness. The comment was made repeatedly in the progress notes that in spite of the cramping pain there was no hyperperistalsis and, in fact, it was thought that the bowel sounds were rather definitely hypoactive. The lungs were clear. There was no significant hepatomegaly and there was no edema. An electrocardiogram was taken shortly before the patient's death.

DR. MASSIE: This eleventh electrocardiogram showed a remarkable change from the previous tracing of September 25, 1954, which we called a normal record; this last one revealed a marked clockwise rotation which indicates that the patient probably had had a pulmonary embolus. She may have had a posterior myocardial infarction or a lateral infarction, but in view of the marked degree of clockwise rotation I would favor the pulmonary embolus as the cause of this electrocardiographic change.

DR. REINHARD: Dr. Massie, this was originally read as showing both pulmonory embolus and myocardial infarction.

DR. MASSIE: I would take away the myocardial infarction and say that pulmonary embolus was the cause of this remarkable change. With the drop in blood pressure one might think that this was a case of terminal myocardial infarction, but when you have electrical axis changes of this degree, a change from a horizontal heart position to almost a vertical heart position, I do not believe one can say the patient had infarction alone. If the patient had an infarction, she also had a pulmonary embolus, but I would prefer to hold to one diagnosis.

DR. REINHARD: Where did this embolus come from, Dr. Massie?

DR. MASSIE: This is a rather strange case. As I listen to the gastroenterologists try to explain abdominal pain here without any objective proof of gastrointestinal trouble, I am reminded of a few patients I have seen with pheochromocytoma; they had abdominal pain and cramping as this patient did. As to where the pulmonary embolus came from, I do not know; perhaps it came from the legs.

DR. REINHARD: Dr. Smith, what do you think was the cause of this patient's electrocardiographic change?

DR. SMITH: I would agree with Dr. Massie entirely; this is a picture of extreme right ventricular enlargement and dilatation probably due to acute pulmonary arterial obstruction. Now whether it was an embolus or whether there was a thrombus formed spontaneously within the pulmonary tree, I do not know. One wonders whether or not there was diffuse vascular disease of some sort going on with so many organ symptoms.

DR. MENDELOFF: In patients of this age and with this amount of vascular disease—if she really had this much over a period of time—one has to think about mesenteric thrombosis. Among the puzzling aspects of this case was the terminal temperature curve which suggested intracerebral rather than intra-abdominal disease, but I should like to have a more detailed account of her abdominal findings. Apparently this pain started low down and ended up as a low, cramping sensation. Finally, she vomited blood. This certainly would have been consistent with mesenteric thrombosis. She apparently passed no blood by rectum.

DR. REINHARD: The description of the abdominal findings is as follows: "abdomen flat and soft with doughy consistency, apparently due to minimally distended colon throughout, moderate tenderness throughout, especially in the left lower quadrant and the right lower quadrant, liver down one fingerbreadth, hypoactive bowel sounds, no rebound tenderness." I must confess that in going over this case I thought mesenteric vascular occlusion, either venous or arterial, was a diagnosis that would have to be very seriously considered. After all, emboli to the mesenteric artery often originate in the heart as a result of myocardial infarction. They may originate in the aorta; they may originate in the pulmonary vein. As far as the clinical picture was concerned, it certainly seemed to be compatible with mesenteric thrombosis. Mesenteric occlusion is characterized by abdominal pain, usually cramping or colicky. This is a symptom which this patient had. Nausea and vomiting occur and tend to be mild. They often subside after a short period of time. The patient may have constipation and diarrhea; there may be moderate distention without abdominal rigidity. Later on the picture changes into one of intestinal obstruction, vomiting of bloody material often occurs, and there may be blood in the stools. The pain becomes constant and very severe. That may have been masked in this case by the unconsciousness. Peristalsis is often hyperactive in the early phase but then becomes hypoactive, and this patient would then fit the later stage of this syndrome. Fever usually occurs, although subnormal temperatures have been reported. Leukocytosis is almost always present and may be very marked, the white count often reaching levels of thirty to forty thousand. This patient's leukocyte count was twenty-two thousand. Shock almost always occurs and usually does not respond to fluid replacement or to other medical procedures. Dr. Smith, does this appeal to you at all?

DR. SMITH: Yes, I would say it is a very reasonable course of events.

DR. JAMES OWEN: I would like to suggest the possibility of a dissecting aneurysm.

DR. REINHARD: That is another possibility we have to consider. Some of the features of this case would fit in with it. First of all, dissecting aneurysm usually occurs in patients who have long-standing hypertension. Furthermore, if the aneurysm involves the ascending aorta, it may compress or dissect along the coronary segments and produce findings compatible with myocardial infarction; however, if that were the case it would have to involve the ascending aorta, and I believe you would anticipate that the patient would have thoracic pain at least early in the process even though the pain might be abdominal later on. The clinical manifestations of a dissecting aneurysm include a sudden onset, the pain reaching maximum intensity usually very quickly, although there is great variability in the pain. Moderate to severe prostration often occurs, with or without loss of consciousness. Death usually occurs within a few hours to a few days although an occasional patient may live even for months. It seems to me that the features against the diagnosis of dissecting aneurysm in this patient are, first of all,

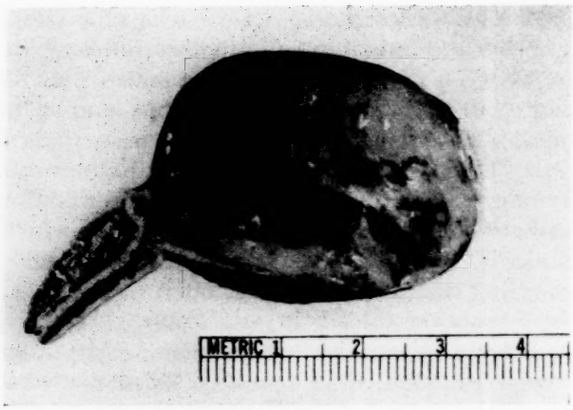


FIG. 1. The gross appearance of the tumor mass in the left adrenal is illustrated. The lesion occupies and replaces the greater part of the organ, only a narrow band of cortical tissue surrounding it at the periphery (light in the photograph). The cut surface of the mass presents a variegated appearance due to an intermixture of areas of necrosis (light) and hemorrhage (dark). The only portion of the adrenal unaffected is shown attached to the tumor below and to the left.

that if you attribute the evidence here for myocardial infarction (if there is such evidence) to an underlying dissecting aneurysm, it would have had to involve the ascending aorta, and the description of the pain was not suggestive of that. Second, how would you account for the guaiac-positive vomitus if the patient had had a dissecting aneurysm? Third, if you say that this patient had a dissecting aneurysm of the aorta to account for her terminal events, there is no very good explanation for the electrocardiographic findings. One would have to say then that she had an independent pulmonary embolus or an independent myocardial infarction. I am assuming, Dr. Schroeder, that the terminal renal events here were just due to shock. Is there any further comment needed on that? The final house staff diagnoses were cholelithiasis; acute cholecystitis, suspected; hypertensive cardiovascular disease; and infarction of myocardium due to arteriosclerotic coronary thrombosis. I personally think this patient had hypertensive cardiovascular disease. I believe she had an infarction of the myocardium due to arteriosclerotic and coronary thrombosis. I am attracted by the possibility that she might have had occlusion of the mesenteric artery due to an embolus from the left ventricle.

PATHOLOGIC DISCUSSION

DR. ROBERT C. AHLVIN: The surface of the body of this well developed, asthenic white woman was not remarkable except for the presence of a well healed, lower abdominal scar. The heart was hypertrophied (470 gm.) and dilated. Coronary arteries were sclerotic and stenosed but not occluded. The myocardium, particularly that of the right ventricle, was diffusely infiltrated with fat, but infarcts were not demonstrable. The lungs were heavy, bright red and crepitant; thrombi were not encountered. Uterus, tubes and ovaries had been removed surgically. The liver was slightly congested. The gallbladder contained two rather large soft stones; its wall was normal and the extrahepatic portion of the biliary tree was widely patent. The surfaces of the kidneys were finely granular, but the organs were otherwise normal.

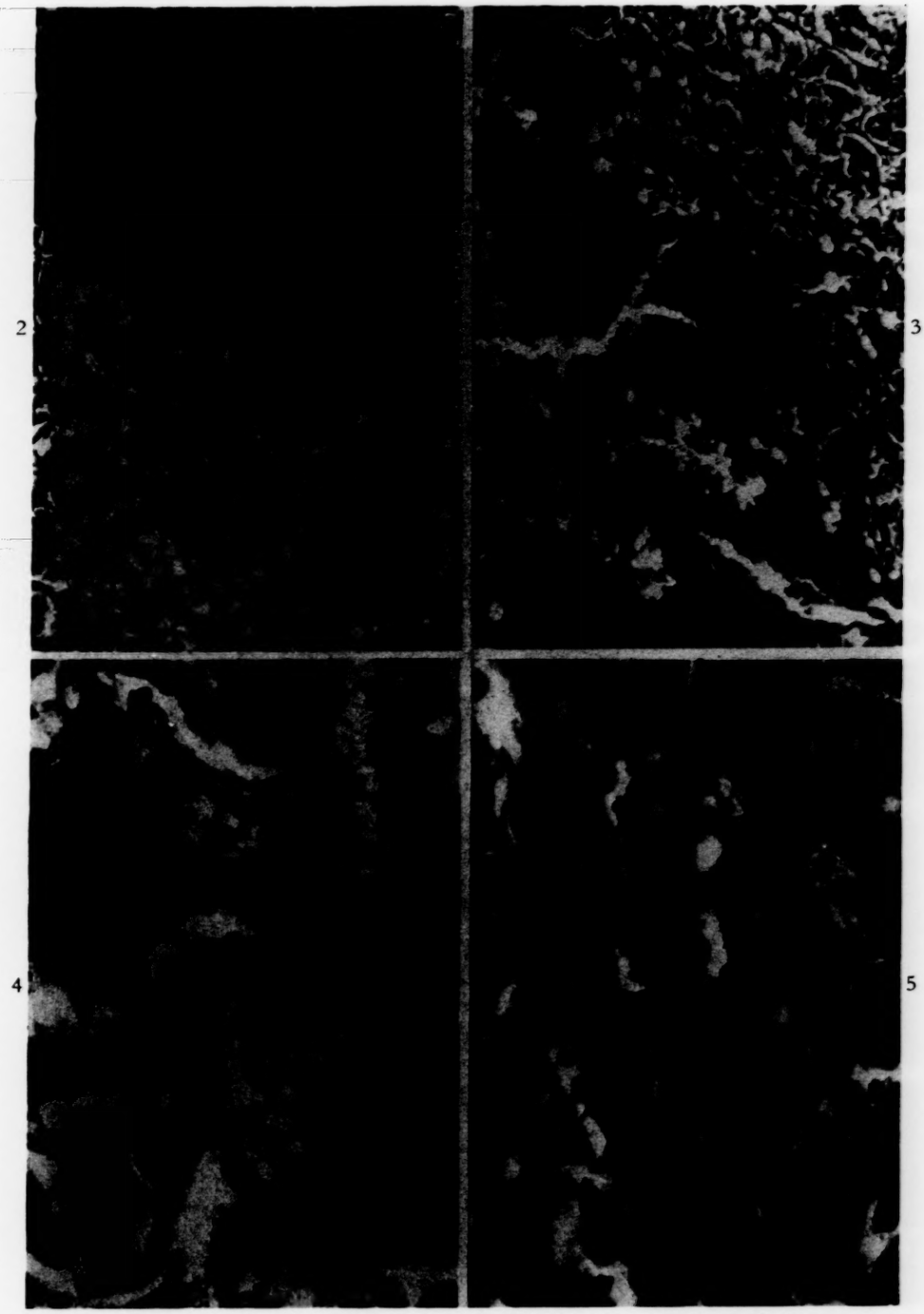
The right adrenal was normal, but the left weighed 50 gm., and had been partially replaced by an orange-yellow mass 4 cm. in diameter (Fig. 1) containing soft, hemorrhagic areas. Bright yellow cortical tissue surrounded the nodule.

DR. W. STANLEY HARTROFT: Microscopically, the tumor in the right adrenal presents a uniform appearance (Fig. 2) interrupted by dilated vessels and hemorrhage. (Fig. 3.) Remnants of cortex at the periphery contain lipid. The cells are arranged in pseudoacini, supported by well defined basement membranes. (Fig. 4.) Nuclei possess prominent nuclear membranes, nucleoli and chromatin; the abundant cytoplasm contains granules. They are blackened by osmic acid and give a positive chromaffin reaction. In many respects the tumor resembles normal adrenal medulla (Fig. 5) and is most certainly a secreting pheochromocytoma. The cortex of the opposite adrenal (left) contains a small adenoma and the organ weighed 10 gm., indicating that it had probably undergone compensatory hyperplasia.

In frozen sections of the heart (left ventricle) stained for lipid, fatty degeneration of the myocardium was appreciable. (Fig. 6.) Fatty infiltration, on the other hand, was unusually prominent in sections of the right ventricle (Fig. 7), although the patient was far from obese (110 pounds). In cases of pheochromocytoma, myocardial degeneration is not infrequently present and may even progress to necrosis.

Renal parenchyma was relatively normal but for minimal degrees of cortical scarring of a nonspecific nature. However, many arterioles exhibited hyperplasia and even necrosis. (Fig. 8.)

Basophils in the anterior pituitary are



FIGS. 2 to 5. These photomicrographs illustrate the appearance of the pheochromocytoma and afford a comparison with the medulla of the contralateral normal adrenal (right). All photographs are of paraffin sections stained with hematoxylin and eosin, photographed through Wratten B and G filters. Figure 2 shows the appearance of one of the better preserved regions of the tumor (original magnification × 200). The acinar arrangement of the cells and large vessels is shown. Figure 3 illustrates another portion of the tumor at the same magnification. Most of the field is taken up by a large area of hemorrhage. A small portion of necrotic tumor tissue occupies the upper right hand corner. Figure 4 illustrates the cytology of the tumor at higher magnification (original magnification × 500). The cells are arranged in acinar forms supported by basement membranes. Note the relation of the tumor cells to the vessel in the upper left. Figure 5 illustrates the appearance of the contralateral, normal adrenal at the same magnification as in Figure 4. The tumor cells closely resemble those of the normal medulla.

FIGS. 6. to 8. These photomicrographs illustrate changes in the cardiovascular system which are probably the result of the hormonal imbalances produced by the secreting tumor cells. Figure 6 is a photomicrograph of a frozen section of left ventricle stained with Oil Red O and Light Green (Wilson). The myocardial fibers are swollen, degenerating and filled with innumerable droplets of stainable fat (black in picture) (original magnification × 400). Figure 7 illustrates fatty infiltration present in the auricles of the heart. There has been extensive replacement of destroyed myocardium by infiltrating adipose tissue Wratten B and G filters; hematoxylin and eosin stain (original magnification × 200). Figure 8 illustrates the appearance of the renal arterioles. To the right of the glomerulus (upper left) is an afferent arteriole cut in cross section. Recent necrosis is present in its media. Below to the left is another portion of the same vessel at the point where it enters the glomerular root. The hyperplastic vacuolated cells probably represent an altered juxtaglomerular unit. The macula densa does not appear in the plane of this section. Masson stain; Wratten B and G filters (original magnification × 500).

vacuolated, enlarged and increased in number. Beta cells of pancreatic islets are normal and their degree of granulation is within normal limits.

This patient suffered from the effects of an adrenal tumor which fulfills all the criteria for the diagnosis of a functional pheochromocytoma. The rest of her organs were unremarkable except that the consequent elevation in blood pressure is reflected by arteriolar hyperplasia with necrosis in the kidney and by cardiac damage (fatty degeneration and fatty infiltration of the myocardium). Vacuolization of basophils is a prominent feature of the pituitary sections and probably resulted from the hormonal imbalance produced by the tumor.

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Case Reports

Anoxemia Secondary to Polycythemia and Polycythemia Secondary to Anoxemia*

O. RATTO, M.D.,
Sao Paulo, Brazil

W. A. BRISCOE, M.D.,
Cardiff, Wales
and
J. H. COMROE, JR., M.D.
Philadelphia, Pennsylvania

J. W. MORTON M.D.
Vancouver, British Columbia

OUR pulmonary function laboratory is often asked to help in determining whether polycythemia is primary in nature or secondary to anoxemia caused by pulmonary disease. Originally we believed that this differential diagnosis could be made solely on the basis of careful measurements of arterial O_2 saturation. This belief was based both on theoretical and practical considerations. Theoretically, uncomplicated polycythemia vera should not lead to arterial anoxemia because diffusion across the normal alveolar capillary membranes permits the transfer of enough O_2 to saturate fully even twice the usual number of red blood cells per unit of blood per unit time. Furthermore, simple pulmonary vascular congestion, which is believed to accompany the plethoric state in polycythemia, should not lead to any decrease in the diffusing capacity of the lungs. Practically, it has been shown that in the great majority of patients with severe polycythemia the arterial O_2 saturation is within normal limits.[1] We have confirmed this in our studies. We considered, therefore, the normal arterial O_2 saturation at rest and during exercise in a patient with polycythemia as strongly suggesting that polycythemia is primary.

It seemed logical to conclude also that reduced arterial O_2 saturation in a patient with polycythemia indicates polycythemia is secondary to anoxemia. However, this conclusion is questionable on several grounds: (1) Patients with polycythemia vera are usually more than fifty years of age. Healthy persons in this age group may have a slight reduction in arterial O_2 saturation.[2] Further, polycythemia vera may coexist in patients with slight to moderate anoxemia caused by pulmonary disease. The problem in these patients is to determine whether the degree of anoxemia present is likely to have caused the degree of polycythemia. (2) Patients with polycythemia vera occasionally have arterial anoxemia which is considered to be secondary to polycythemia itself.[3–5]

This paper contains a report of a patient with polycythemia referred to us by another doctor† who wished to know whether the polycythemia in this patient was secondary to anoxemia. Arterial blood studies showed that the patient was indeed anoxemic and this suggested that he had secondary polycythemia. However, more complete studies led to the conclusion that anoxemia was caused by localized damage to the medullary respiratory center, possibly caused by emboli or thromboses.

We are also reporting briefly on twenty-four other patients with polycythemia vera who had little or no arterial anoxemia or pulmonary disorders; we wish to stress that anoxemia secondary to polycythemia vera is uncommon and not, as might be inferred from a recent report,[5] a frequent occurrence.

CASE REPORT

Patient N. M. was a large man (S. A. = 2.1 sq. M), sixty-three years old. His first complaints were in 1937 when he developed frequent hiccoughs, sometimes

† Dr. Rodney Kirk of the York Hospital.

* From the Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. Supported in part by a contract between the office of Naval Research and the University of Pennsylvania.

followed by vomiting and blood spitting. However, he was able to work regularly on a farm until July, 1953 when he had a severe hemorrhage, possibly originating in esophageal varices. He also complained of arthritis and, a few months later, of numerous attacks of numbness and tingling on the right side of his body associated with a failing memory. He had no dyspnea except for a short time in June, 1953. Pertinent findings on physical examination were purplish-red cyanosis of the face, numerous telangiectasia, moderate enlargement of the heart and liver (spleen was not palpable), venous engorgement in the optic fundi and Argyll-Robertson pupils. Serum and cerebrospinal fluid tests for syphilis gave negative results and cerebrospinal fluid pressure was within normal limits. X-ray of the chest showed increased markings throughout the lung fields; these were attributed to mild passive congestion. Studies of the blood performed after the severe hematemesis showed: red cells, 6.0 to 6.4 million per cu. mm.; hemoglobin, 20.0 to 20.6 gm./100 ml.; hematocrit, 67 to 70 per cent; white blood count, 6850 to 14,2000/cu. mm. and platelets, 140,000 to 174,000/cu. mm. The measurements that were made on this patient are presented in Tables I and II.

TABLE I
PULMONARY FUNCTION STUDIES ON PATIENT N. M.

Studies	Normal	Patient N. M.
Lung Volumes:		
Inspiratory capacity (ml.)	3,280	3,490
Expiratory reserve (ml.)	820	610
Vital capacity (ml.)	4,100	4,120
Residual volume (ml.)	1,840	1,930
Total lung capacity (ml.)	5,940	6,030
RV/TLC × 100 (%)	42	32
Functional residual capacity (ml.)	2,660	2,540
Respiratory dead space (ml.)	180–200	270
Distribution of Inspired Gas:		
Single breath O_2 test (% N_2)	2.0	1.3
Pulmonary N_2 emptying rate, 7′ test (% N_2)	2.5	0.3
Diffusion:		
Fractional CO uptake (%)	50	48
Diffusing capacity, single breath (ml. CO/min./mm. Hg)	20–40	30
Mechanics:		
Maximum breathing capacity (L./min.)	107	194
1 second vital capacity (%)	81	79
3 second vital capacity (%)	95	92
Maximum expiration flow rate (L./min.)	500	440
Maximum inspiration flow rate (L./min.)	400	202
Miscellaneous:		
O_2 consumption (ml./min.)	300	370
Hematocrit (%)	46	64.2
Hemoglobin (gm./100 ml.)	15.6	18.6
O_2 capacity (ml. O_2/100 ml.)	20.9	24.9
Venous pressure (cm. H_2O)	4–11	8.0
Circulation time, lung to ear (sec.)	6–8	9
Circulation time, arm to ear (sec.)	12–16	20

TABLE II
BLOOD GAS AND VENTILATORY STUDIES ON PATIENT N. M.

Blood Gas Studies	9/29/53	11/10/53	6/10/54
Arterial O_2 saturation (air), %	82	74	62
Arterial O_2 saturation (hyperventilation, air), %	.....	99	.....
Arterial O_2 saturation (O_2), %	100	100	99.8
Arterial O_2 saturation (exercise), %	.....	58	.....
Arterial O_2 saturation (breath-holding), %	.....	35	.....
Arterial O_2 saturation (7.5% CO_2 in air), %	.....	88	.....
Arterial P_{CO_2}, mm Hg (air)	75	68	62
Arterial pH (air)	7.24*	7.20	7.29
Ventilatory Studies	**9/29/53**	**11/10/53**	**6/10/54**
Respiratory minute volume (L./M^2/min.)	4.8	6.1	3.8
Tidal volume (L./M^2/min.)	0.218	0.200	0.136
Respiratory (breaths/min.)	22	30	28
Alveolar ventilation (L./M^2/min.)	1.7	1.8	0.056

* This patient was not able to compensate for the respiratory acidosis; the reasons for this have not been explored.

In our laboratory we classify pulmonary disorders on the basis of alterations in physiologic processes as follows:[6]

1. Disorders of ventilation
   - A. Hypoventilation
   - B. Uneven distribution of inspired gas (in relation to pulmonary capillary blood flow)
2. Impairment of diffusion of gases across alveolar capillary membranes
3. Disorders of pulmonary circulation
   - A. Uneven distribution of pulmonary capillary blood flow (in relation to alveolar ventilation)
   - B. Venous-arterial shunt
4. Abnormalities in erythrocytes or hemoglobin

It soon became apparent that hypoventilation was a major factor in this patient. The evidence was as follows: (1) The patient had CO_2 retention as well as anoxemia. (2) His resting alveolar ventilation [(tidal volume − respiratory dead space) × frequency] was abnormally low in relation to his O_2 consumption. In part this was due to a moderate enlargement of the anatomic dead space to 270 ml. (as measured by the single breath test using the nitrogen meter[7]) but in

larger measure was due to a reduction in tidal volume. (3) The anoxemia in this patient could be relieved by voluntary hyperventilation with air. When he breathed at different tidal volumes (frequency maintained relatively constant), the arterial O_2 saturation became normal for a man of his age group when the alveolar ventilation reached normal values of about 4.0 liters.* (Table III.) When no attempt was made to regulate his breathing, the total ventilation and alveolar ventilation were variable and the arterial O_2 saturation fluctuated widely with the alveolar ventilation.

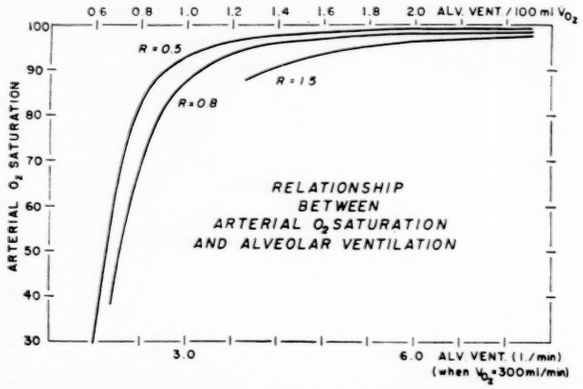

FIG. 1. Relationship between alveolar ventilation and arterial O_2 saturation; these data are derived from the alveolar air equation and the standard oxygen dissociation curve. The data for the bottom scale of alveolar ventilation (V_A) apply when oxygen consumption (V_{O_2}) is 300 ml./minute; those for the upper scale apply to the alveolar ventilation in liters/minute for each 100 ml. O_2 consumption/minute. The values for the arterial O_2 saturation are the maximal possible values at each level of alveolar ventilation because it is assumed that the arterial O_2 tension equals the alveolar O_2 tension. A low respiratory quotient tends to raise the saturation produced by any given alveolar ventilation, but the effect is relatively small. It is meaningless to plot saturations of patient N. M. on this diagram because we do not know the oxygen consumption and respiratory quotient during hypoventilation, nor do we know that the patient was in a steady state. However, the diagram illustrates the theoretic basis for the experimental finding that during hypoventilation arterial saturation is very sensitive to small changes in alveolar ventilation. (Table III.)

In normal subjects the sensitivity of the respiratory center to an increase in arterial P_{CO_2} prevents hypoventilation and anoxemia. When arterial O_2 saturation is maintained in the normal range of 95 to 98 per cent large increases in ventilation produce only slight changes in saturation. But when the respiratory center permits hypoventilation, as was the case here, the arterial saturation is greatly changed by small changes in ventilation. This is illustrated by Figure 1 in which alveolar ventilation is plotted against the maximal possible saturation which it could produce.

Despite this evidence, it seemed important to exclude other pulmonary disorders as contributing to this anoxemia.

TABLE III

EFFECT OF VARIATIONS IN ALVEOLAR VENTILATION UPON ARTERIAL O_2 SATURATION

Respiratory Minute Volume (ml.)	Respiratory Frequency (f)	Tidal Volume (T. V.) (ml.)	Alveolar Ventilation/Breath (TV − DS)* (ml.)	Alveolar Ventilation/Minute (TV − DS) × f (ml.)	% Saturation Arterial Blood (oximeter reading)‡
4,060	22	185	.....†	.....†	55
4,400	22	200	.....†	.....†	65
5,060	24	210	.....†	.....†	80
5,060	24	210	.....†	.....†	65
6,440	24	270	0	0	74
6,530	23	285	15	345	89
6,780	24	285	15	360	84
7,010	25	280	10	250	87
7,240	25	290	20	500	82
8,320	28	295	25	700	86
9,330	26	360	90	2,350	87
9,630	27	355	85	2,300	90
9,680	26	370	100	2,600	89
11,600	29	400	130	3,770	94
12,100	31	390	120	3,720	93
17,450	30	580	310	9,300	95.5
22,400	28	800	530	14,800	97
24,500	29	845	575	16,650	96
24,700	29	850	580	16,800	97
24,150	25	965	695	17,350	96
41,000	28	1,465	1,195	33,500	97
60,400	26	2,320	2,050	53,300	96

* A dead space value of 270 ml. is used in these calculations although it is probably greater at large tidal volumes and less at small tidal volumes.

† When alveolar ventilation is computed in these cases from values for tidal volume and anatomic dead space, negative values are obtained. This occurs because inspired gas does not push the dead space gas ahead of it as a square front but pushes into the dead space as a wedge or cone so that some inspired gas reaches the alveoli before a volume equal to dead space volume has been inspired. Therefore, when tidal volume is so small that it does not completely flush the dead space, the alveolar ventilation/breath is considerably greater than TV − DS.[8] Thus estimates of alveolar ventilation given in the upper half of this table are underestimates.

‡ The arterial O_2 saturations recorded in the table are all "oximeter" saturations. The patient was not necessarily in a steady state since the different rates of ventilations were maintained for only two or three minutes in some cases.

Uneven distribution of inspired gas to the alveoli was excluded by the single breath test utilizing the nitrogen meter[9] and by the pulmonary nitrogen emptying rate test. Furthermore, the lung volumes, RV/TLC ratio, maximum breathing capacity and maximal inspiratory and expiratory flow rates were all within normal limits.

Impairment of diffusion was ruled out by two tests of CO uptake.[10,11] Furthermore, the arterial P_{CO_2} of 75 mm. Hg was incompatible with uncomplicated alveolar-capillary block.

* It is of interest that an increase in alveolar ventilation, produced by inhalation of 7.5 per cent CO_2, did not raise the arterial O_2 saturation of this patient to the expected value; this may be due in part to the acidosis produced, with a consequent shift in the O_2 dissociation curve.

It is possible that multiple pulmonary emboli, thromboses or sludges might produce anoxemia owing to uneven distribution of pulmonary capillary blood flow, even though distribution of inspired gas to the alveoli was uniform. However, calculations of dead space based on Bohr's equation and measurements of arterial and expired P_{CO_2} showed that the dead space volume so computed (240 ml.) was approximately the same as the anatomic dead space (270 ml.). This indicates that the ventilation/blood flow ratios of this patient were not widely different in different parts of the lungs; since ventilation was uniform by the single breath test it is reasonable to assume that the pulmonary capillary blood flow was also fairly uniform throughout the lungs.

Venous arterial shunts were excluded as an important factor by the observation that the blood became fully saturated during hyperventilation with air or during the inhalation of 100 per cent O_2. To eliminate completely the possibility that a small shunt is present, not only should the hemoglobin of arterial blood become fully saturated with O_2 during the inhalation of pure O_2, but an additional 2.0 ml. O_2/100 ml. blood should be present as dissolved O_2. This latter value was never quite attained in our studies on patient N. M. so that a small shunt was not ruled out; however, it could not possibly explain the degree of unsaturation in this case.

Abnormal hemoglobin could not be detected by spectrophotometric studies.* The oxyhemoglobin dissociation curve was normal, considering the arterial pH, and studies of the rate of uptake of CO by the red blood cells showed this to be within normal limits.

These studies confirmed our impression that hypoventilation was the patient's major difficulty. Our next step was to determine the reason for the hypoventilation. The fact that the patient had decreased alveolar ventilation despite the coexistence of three potent stimuli to respiration (anoxemia, acidosis and increased arterial P_{CO_2}) indicated that either there was a serious mechanical hindrance to breathing or that the neuromuscular mechanisms responsible for breathing were depressed. Clearly, since the patient had a maximum breathing capacity of 190 L./minute, there was neither mechanical limitation to breathing nor depression of his peripheral neuromuscular mechanisms, and the lesion, by exclusion, must be in the central respiratory mechanism. This was confirmed by several tests.

1. The patient had an unusually sluggish respiratory response to inhalation of CO_2 on four occasions. The respiratory minute volume increased to only 14 to 21 L./minute even after breathing 7.5 per cent CO_2 for twenty minutes. Dripps and Comroe[12] found that healthy young men responded to the inhalation of 7.6 per cent CO_2 by increasing their minute volume to 52 L./minute (standard deviation ± 15.4). There was considerable individual variation in the response of this group but the response of our patient was less than the mean minus 2 standard deviation. Morton[13] found that the average minute volume during inhalation of 7.2 per cent CO_2 in air was 50 L./minute (standard deviation ± 16.3) and that practically every subject developed dyspnea and headache during inhalation; our patient had no complaints during inhalation of 7.5 per cent CO_2 for more than twenty minutes.

2. Starr and associates[14] found that adrenalin® increases respiratory minute volume; this is believed to be due to direct stimulation of the respiratory center. Subcutaneous injection of 0.5 mg. adrenalin produced no change in respiratory minute volume in the patient.

3. Our patient's respiratory response to exercise was also poor, and arterial O_2 saturation fell markedly. (Table II.) This, added to the finding that ventilation was voluntary at a rate of 190 L./minute, suggests that the voluntary hyperventilation did not require participation of the medullary respiratory center that is responsive to CO_2, acidosis or anoxemic reflexes, but that the hyperpnea of muscular exercise did.

4. The patient also had an abnormal response to breath-holding. He was able to hold his breath for ninety seconds and experienced no serious discomfort during this period. The test was discontinued because of the development of extreme cyanosis; arterial blood drawn after eighty seconds of breath holding showed the arterial O_2 saturation to be 35 per cent at that time and the P_{CO_2} 77 mm. Hg. This failure to respond to anoxemia strengthens the belief that the respiratory response to stimuli from the carotid and aortic chemoreceptors was also reduced.

There seemed to be no depression of the medullary vasomotor center because the patient did not have postural hypotension and responded normally to the feet-down tilt and cold pressor tests. No neurophysiologic abnormalities could be detected: the electroencephalogram was normal and his pain threshhold* was within normal limits.

We have studied many patients with severe anoxemia, acidosis and CO_2 retention in whom hyperventilation was not possible either because of mechanical limitation or because of narcosis. This is the first patient we have observed who was ambulatory, highly cooperative and normal with respect to physiologic tests of his lungs, yet who failed to respond to these stimuli. For this reason we believe he had a lesion in the region of the respiratory center. This lesion might be due to (1) thromboses resulting from primary polycythemia or (2) a primary neurologic or cerebral vascular lesion leading to chronic depression of respiration, chronic anoxemia and secondary polycythemia. The chief complaint of hiccoughs, dating from 1937, may be supportive evidence of the existence of a lesion in the region of the respiratory center. However, we have no way of determining the cause of the lesion during the lifetime of the patient.

* Performed by Dr. David Drabkin.

* Tested by Dr. James Hardy.

TABLE IV

PULMONARY FUNCTION STUDIES IN PATIENTS WITH POLYCYTHEMIA VERA

Initials of Patients	Age (yr.)	Height (inches)	Weight (lb.)	BSA M^2	Sex	Red Blood Count (million/cu. mm.)	Hemoglobin (gm./100 ml.)	Hematocrit (%)	Vital Capacity		Residual Volume		Total Lung Capacity		RV/TLC × 100	Maximum Breathing Capacity		Alveolar Gas Distribution (% N_2) ‡	Seven Minute Washout (% N_2) §
									ml.	%†	ml.	%†	ml.	%†		L./M^2/min.	%†		
W. B.	70	57	100	1.35	F	10.3	18.7	73	1,830	97	.....	...	.....	...	..	37.3	89	1.3	2.0
J. McA.	21	65	105	1.49	F	....	20.1	..	2,710	82	.....	...	.....	...	..	55.7	91	1.0	1.0
R. C.	47	63	120	1.54	F	10.0	21.3	74	2,605	91	.....	...	.....	...	..	23.2	46	...	1.5
F. B.*	55	62	118	1.52	F	6.4	15.8	..	2,280	90	.....	...	.....	...	..	39.1	93	...	...
Y. S.*	75	67	106	1.53	F	....	14.4	..	1,945	104	.....	...	.....	...	..	31.3	75	...	...
B. D.	55	64	130	1.61	M	....	20.7	69	2,980	80					..	60.5	138	1.2	2.0
H. B.	45	69	144	1.78	M	7.0	16.3	55	4,155	95	.....	...	.....	...	..	61.3	94	...	...
M. B.	56	63	138	1.64	F	....	18.4	61	3,230	126	.....	...	.....	...	..	31.4	75	1.5	1.3
J. T.	45	67	186	1.95	M	8.0	17.0	51	3,990	94	.....	...	.....	...	..	62.3	100	...	...
H. R.	63	63	137	1.61	F	11.0	17.0	61	2,360	113	1,260	52	3,620	80	35	29.6	70	1.0	0.5
M. K.	65	64	105	1.44	F	6.1	18.7	61	1,790	85	2,410	99	4,200	92	57	32.0	76	1.4	1.6
P. S.	61	65	132	1.62	M	8.0	17.5	72	3,700	100	2,955	123	5,915	97	50	38.4	87	4.0	2.8
E. V.	61	64	146	1.70	F	....	17.8	64	2,300	109	.....	...	.....	...	..	55.7	113	0.6	1.0
W. K.*	36	68	186	1.95	M	....	16.0	52	3,820	89	1,130	86	4,950	88	23	73.4	109	1.0	1.0
P. M.*	30	67	154	1.79	M	6.5	16.0	48	4,460	105	740	69	5,200	98	14	62.7	89	0.9	0.5
M. N.	57	63	127	1.58	F	8.2	22.4	73	2,660	104	1,655	68	4,315	85	38	60.5	144	1.0	1.4
L. W.*	56	62	180	1.81	M	....	16.1	56	3,650	101	.....	...	.....	...	..	66.9	152	...	3.0
H. W.	59	71	205	2.11	M	....	17.7	56	2,260	60	.....	...	.....	...	..	62.5	142	1.5	...
G. H.*	53	61	161	1.70	F	....	13.4	44	2,480	100	2,395	99	4,875	99	49	38.3	94	1.0	2.5
D. S.	62	65	133	1.65	F	....	18.7	61	2,750	128	915	38	3,665	80	25	46.5	111	1.4	1.5
C. R.	50	63	158	1.78	F	....	18.7	69	3,320	87	2,074	85	5,394	86	38	73.0	174	0.5	0.2
A. L.	69	70	136	1.75	M	7.6	18.6	63	3,870	104	2,462	101	6,332	102	39	37.0	84	2.4	0.9
C. B.	44	75	226	2.30	M	4.5	18.0	51	5,200	109	1,357	93	6,557	105	21	54.5	65	1.3	3.0
F. W.*	47	71	198	2.08	M	....	16.2	45	.....	...	.....	...	.....	...	..	....	...	...	...

* Blood studies performed after therapy for polycythemia.

† % equals per cent of predicted value based on physical characteristics and age.

‡ Normal values for alveolar gas distribution are less 1.5 per cent N_2.

§ Normal values for seven minute washout are less than 2.5 per cent N_2.

We have followed up the patient for more than nine months. During this time therapy has included bleeding, mechanical hyperventilation continuously for as long as four days, O_2 therapy, diamox® and the use of sympathomimetic drugs which have a stimulant effect on the central nervous system. None of these has increased the resting ventilation or respiratory response to CO_2. Arterial saturation was lower during the last study and we suspect that the depression of the central nervous system is not only irreversible but may have become worse because of chronic anoxia and CO_2 retention.

TABLE V

ARTERIAL BLOOD STUDIES IN PATIENTS WITH POLYCYTHEMIA VERA

Initials of Patients	Arterial Blood Studies						
	O_2 Content (vols. %) Rest	O_2 Capacity (vol. %) Rest	O_2 Saturation (%)			P_{CO_2} (mm. Hg) Rest	pH Rest
			Rest	Exercise	100% O_2*		
W. B.	24.9	25.0	99.6	....	.....	37.0	7.39
J. McA.	26.3	26.9	97.5	....	.....	34.5	7.42
R. C.	27.4	28.5	96.7	....	.....	38.5	7.40
F. B.	20.7	21.2	97.4	....	.....	40.8	7.36
Y. S.	17.8	19.3	92.3	....	.....	43.0	7.37
B. D.	26.8	27.7	95.8	....	.....	41.0	7.35
H. B.	21.1	21.8	96.7	....	.....	40.0	7.37
M. B.	23.0	24.7	94.0	....	.....	36.0	7.48
J. T.	21.9	22.8	96.1	....	.....	43.0	7.35
H. R.	21.5	22.8	94.5	....	.....	41.8	7.37
M. K.	23.5	25.1	93.7	....	$100^{+1.5}$	42.0	7.39
P. S.	22.1	23.4	94.7	93.4	$100^{+1.79}$	46.9	7.34
E. V.	23.5	23.8	98.5	....	$100^{+1.81}$	28.0	7.45
W. K.	20.8	21.4	97.0	....	.....	46.0	7.37
P. M.	20.7	21.4	96.6	96.2	$100^{+1.39}$	39.0	7.38
M. N.	29.1	30.0	97.3	95.9	$100^{+2.3}$	35.5	7.37
L. W.	21.2	21.6	98.2	....	.....	36.3	7.45
H. W.	24.2	23.7	95.8	96.2	.....	....	....
G. H.	17.8	17.9	99.0	98.4	$100^{+1.67}$	38.5	7.40
D. S.	23.8	25.0	95.0	95.5	.....	41.0	7.37
C. R.	24.1	25.0	96.0	97.5	$100^{+1.53}$	37.0	7.39
A. L.	24.1	24.9	96.0	92.0	$100^{+2.56}$	37.0	7.37
C. B.	23.2	24.1	96.0	....	$100^{+1.33}$	35.0	7.42
F. W.	19.9	21.7	92.0	98.0	.....	42.0	7.38

* Superscript refers to ml. O_2/100 ml. blood in excess of that required to saturate hemoglobin (i.e., dissolved O_2).

PULMONARY FUNCTION IN PATIENTS WITH POLYCYTHEMIA VERA

Over a period of several years we have studied twenty-four patients who satisfied the criteria of the hematology section for diagnosis of polycythemia vera. (Table IV.†) Arterial O_2 saturation and pulmonary function studies gave normal results in all of these except for one in which the subject appeared to have some coexisting emphysema; however, the arterial O_2 saturation was normal for a sixty year old man, both during rest and exercise. The patient was considered to have had polycythemia vera. (Table V.)

In this group of twenty-four patients vital capacity was 80 per cent or more of the predicted value in twenty-three, maximum breathing capacity was 80 per cent or more of predicted value in seventeen and arterial P_{CO_2} was 43 mm. Hg or less in all but two. The ratio RV/TLC was measured in eleven patients and was normal for the age group in all but one. Distribution of inspired gas was measured in nineteen and was normal in all. Arterial O_2 saturation was measured during exercise in nine; it decreased below the resting value in only one. The uptake

† On request more complete data can be obtained from the American Institute of Documentation.

of carbon monoxide (a test of diffusion across the alveolar capillary membranes) was normal in all four patients tested.

These studies are included to show that serious derangement of pulmonary function is the exception rather than the rule in polycythemia vera. A gross abnormality was found in only one (N. M.) of the twenty-five patients studied, and we cannot yet determine whether the pulmonary disorder was primary or secondary.

Possible disturbances in pulmonary function which may be caused by polycythemia vera are:

1. *Central effects:* Depression of the respiratory center owing to sludging or thrombosis can lead to CO_2 retention, anoxia and further central depression.

2. *Effects on the lungs:* An overload of the oxygenating mechanism has been postulated but probably does not occur because total O_2 transfer per minute is not increased in this disease.

A. *Decrease in diffusing capacity:* Emboli or thrombosis may decrease the pulmonary capillary bed and so decrease the diffusing capacity of the lungs. Vascular congestion may decrease the vital capacity and maximum breathing capacity, but should not impair diffusion.

B. *Variations in the ventilation/blood flow ratios throughout the lungs:* It has been suggested that increase in blood volume may open additional capillaries, increase blood flow in these areas and so distort the normal relationship between alveolar ventilation and pulmonary capillary blood flow.[5] Embolization of part of the pulmonary vascular bed would also lead to alterations in these ratios in different parts of the lungs.

3. *Effects on the thorax:* Sluggish blood flow, caused by increased blood viscosity might lead to easy fatigue on the part of the respiratory muscles and a reduction in maximum breathing capacity. However, many patients with severe polycythemia have a normal maximum breathing capacity. The maximum breathing capacity will certainly be reduced in semicomatose patients or patients sick from other causes.

It appears important, despite the rarity of pulmonary and respiratory derangements in polycythemia vera, to measure pulmonary function more frequently in such patients, with particular emphasis on the reactivity of the respiratory center. Patient 4 of Newman et al.[5] was obviously somnolent, lethargic and apathetic and patient 5 of the same series had an incapacitating degree of lethargy. In such cases central depression is readily recognizable. In our patient there was no indication of central depression except for the inability of the respiratory center to respond to certain characteristic stimuli. Our studies also indicate the value of making estimates of alveolar ventilation as well as measuring the minute volume of breathing.

TABLE VI

HEMOGLOBIN AND HEMATOCRIT VALUES IN PATIENTS WITH CHRONIC ANOXEMIA CAUSED BY PULMONARY DISEASE

Number of Patients	% Arterial O_2 Saturation		Hemoglobin (gm./100 ml.)		Hematocrit (% cells)	
	Mean	Range	Mean	Range	Mean	Range
5	46.2	26.8–59.0	13.8	9.2–16.4	47.6	32.5–56.0
9	75.7	70.2–79.9	13.9	9.8–18.8	48.6	37.6–63.0
29	86.6	80 –89.9	14.2	9.2–16.8	46.8	35.0–57.0
71	92.7	90.2–95.3	13.6	9.8–17.1	43.5	32.0–54.5

DEGREE OF SECONDARY POLYCYTHEMIA IN PATIENTS WITH ANOXEMIA

Because chronic pulmonary disease with anoxemia and secondary polycythemia is found frequently in the same age group as is polycythemia vera, we believe it may be helpful to record here our experience with patients with secondary polycythemia to indicate the degree of polycythemia associated with chronic pulmonary disease. Our data are included in Table VI. We have excluded patients with right to left shunts associated with congenital heart disease or pulmonary hemangiomas; in these, the red blood cell count, hemoglobin and hematocrit values have been uniformly high unless a hemorrhage has occurred. In our patients with chronic pulmonary disease the hemoglobin values rarely exceed 16.5 gm./100 cc. and the hematocrit usually does not exceed 55 per cent. Factors which limit the polycythemic response in patients with anoxemia caused by chronic pulmonary disease may be (1) increased arterial P_{CO_2} values, which occur in many patients with uneven ventilation in relation to pulmonary capillary blood flow, and (2) chronic pulmonary infection.* On clinical grounds alone,

* Hurtado et al.[15] studying residents of high altitude, have found that the polycythemic response is depressed when anoxemia is severe (arterial O_2 saturation less than 60 per cent). We have not observed a similar effect in patients with severe anoxemia owing to venous-arterial shunts at sea level.

if venous-arterial shunts have been excluded, the diagnosis of polycythemia vera is likely in any patient who has a hematocrit greater than 60 per cent and a hemoglobin which exceeds 17 gm./100 cc.

SUMMARY

Pulmonary function studies on a patient with polycythemia, arterial anoxemia and CO_2 retention showed that lung volumes, distribution of inspired air, distribution of pulmonary capillary blood, alveolar-capillary diffusion and mechanics of breathing were within normal limits. The only respiratory defect was an inability to ventilate involuntarily sufficiently to arterialize the venous blood. By exclusion a diagnosis of specific depression of the medullary respiratory center was made. It is not known whether the postulated central lesion is primary or is secondary to thromboses related to polycythemia.

The respiratory and pulmonary disorders which might be caused by polycythemia are discussed. In our experience these have been infrequent. Data obtained in this laboratory on the degree of secondary polycythemia associated with anoxemia of pulmonary origin are summarized.

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Adrenal Cortical Carcinoma Producing Solely Mineralocorticoid Effect*

LAURANCE V. FOYE, JR., M.D. *and* THOMAS V. FEICHTMEIR, M.D.
San Francisco, California

THE familiar clinical syndromes produced by adrenal cortical hyperfunction are frequently associated with varying degrees of electrolyte and water imbalance. These abnormalities, consisting of sodium retention, increased potassium excretion, expansion of the blood volume and, frequently, hypertension, have been reproduced in experimental animals and man by the administration of large doses of 11-desoxycorticosterone[1] or with aldosterone.[2,3] The metabolic and virilizing abnormalities typical of the spontaneously occurring syndromes are not produced by the experimental use of the mineralocorticoids.

The production of electrolyte and water defects by adrenal cortical hyperfunction or tumors in the absence of the metabolic or virilizing effects has not been reported. The authors had the opportunity of studying a patient with an adrenal cortical carcinoma producing solely mineralocorticoid effect, presumably due to excessive aldosterone secretion.

METHODS

The patient was maintained on a diet providing 5 gm. sodium chloride daily throughout his hospitalization. Daily collections of twenty-four-hour urine specimens were made and serum sodium, potassium, chlorides and CO_2 analyses were performed daily during each period of changing clinical state or therapy. Analyses made on the urines included sodium, potassium, chloride, creatinine, 17-ketosteroids and total or free corticoids. During periods of relative stability in the clinical status these measurements were performed two to three times each week.

Blood volumes were determined by the radiochromium-tagged red cell method.[4] Excretion of 17-ketosteroid in the urine was measured by the method reported by Drekter et al.[5] The Porter-Silber method[6] was used to measure urinary free corticoids and the method of Norymberski[7] was used to determine total corticoids (17-ketogenic steroids).

CASE REPORT

Patient H. W., a sixty year old Negro man, entered the hospital on November 20, 1953, complaining of inability to walk for the previous eight or nine days. He stated that he had been in good health until approximately eight months prior to entry when he noted the gradual onset of severe thirst, polyuria and polydipsia. His appetite remained good and there was no weight loss. Approximately nine days prior to entry he noted the onset of rapid progression of aching and weakness in all extremities. He became unable to lift his arms above the horizontal position or to lift his feet from the floor when standing. There had never been any previous similar episodes.

On his three previous admissions (for hemorrhoidectomy and anoplasty) dating from May to October 1953, the urine was consistently negative for sugar and acetone, and fasting blood sugars were normal on two occasions. An electrocardiogram taken in July 1953, showed "LVH with persistent high U waves." The patient had been hypertensive on all previous admissions. The blood pressure ranged from 200/135 to 176/110. The specific gravity of his urine never exceeded 1.009. Serum urea nitrogen and creatinine determinations were normal on two occasions. In July 1953, a twenty-four-hour urine specimen measured 3,520 cc. and the creatinine clearance was 81 cc. per minute.

Physical examination revealed a well developed, moderately obese, ruddy-faced, elderly

* From the Medical and Pathology Services, Veterans Administration Hospital, San Francisco, Calif., and the University of California and Stanford University Medical Schools.

FIG. 1. The patient in December, 1953; note the absence of "cushingoid" features.

man (Fig. 1), complaining of severe thirst. Blood pressure was 175/112.

The skin was warm and dry and the mucous membranes were very dry. There was no lymphadenopathy and no venous distention. The eyegrounds showed moderate A-V nicking and generalized arteriolar narrowing. The lungs were clear. The heart was enlarged 3 cm. to the left of the mid-clavicular line in the sixth intercostal space; rhythm was normal and no murmurs were heard. The abdomen was soft, without striae or masses. The liver was 1.5 cm. below the right costal margin on inspiration and was non-tender. The spleen was not felt. The genitalia were normal. Deep muscle reflexes were markedly hypoactive, especially the biceps and quadriceps. Muscle power was markedly decreased without evident wasting. The patient was unable to rise from a sitting position. The sensory system was normal.

Laboratory studies on entry were as follows: white cells, 7,800; differential: neutrophils, segmented 78 per cent; non-segmented 3 per cent; lymphocytes, 17 per cent; monocytes, 2 per cent; hemoglobin, 15.1 gm. per cent; packed cell volume, 42 cc. per cent; and corrected sedimentation rate, 11 mm. per hour. Urinalysis revealed a pH of 6.5; specific gravity, 1.005; albumin, trace; sugar, negative; acetone, negative; and centrifuged sediment, negative. Kahn and Kolmer tests were negative. Blood chemistries were as follows: urea nitrogen, 10.0 mg. per cent; creatinine, 1.3 mg. per cent; fasting blood sugar (Somogyi), 71 mg. per cent; blood sugar two hours postprandial, 89 mg. per cent; albumin, 2.4 gm. per cent; globulin, 1.8 gm. per cent; total cholesterol, 222 mg. per cent; cholesterol esters, 134 mg. per cent; sodium, 150 mEq./L.; potassium, 1.8 mEq./L.; chlorides, 90 mEq./L.; CO_2 53 mEq./L.; serum calcium, 4.55 mEq./L.; phosphorus, 0.74 mM./L.; alkaline phosphatase, 3.8 units (King-Armstrong). Arterial oxygen saturation 87.0 per cent; venous oxygen saturation 79.5 per cent. Fasting eosinophil count, 36 and 12 per cu. mm. on separate occasions. X-ray of the chest revealed only moderate left ventricular enlargement. Skull x-rays were normal. Intravenous

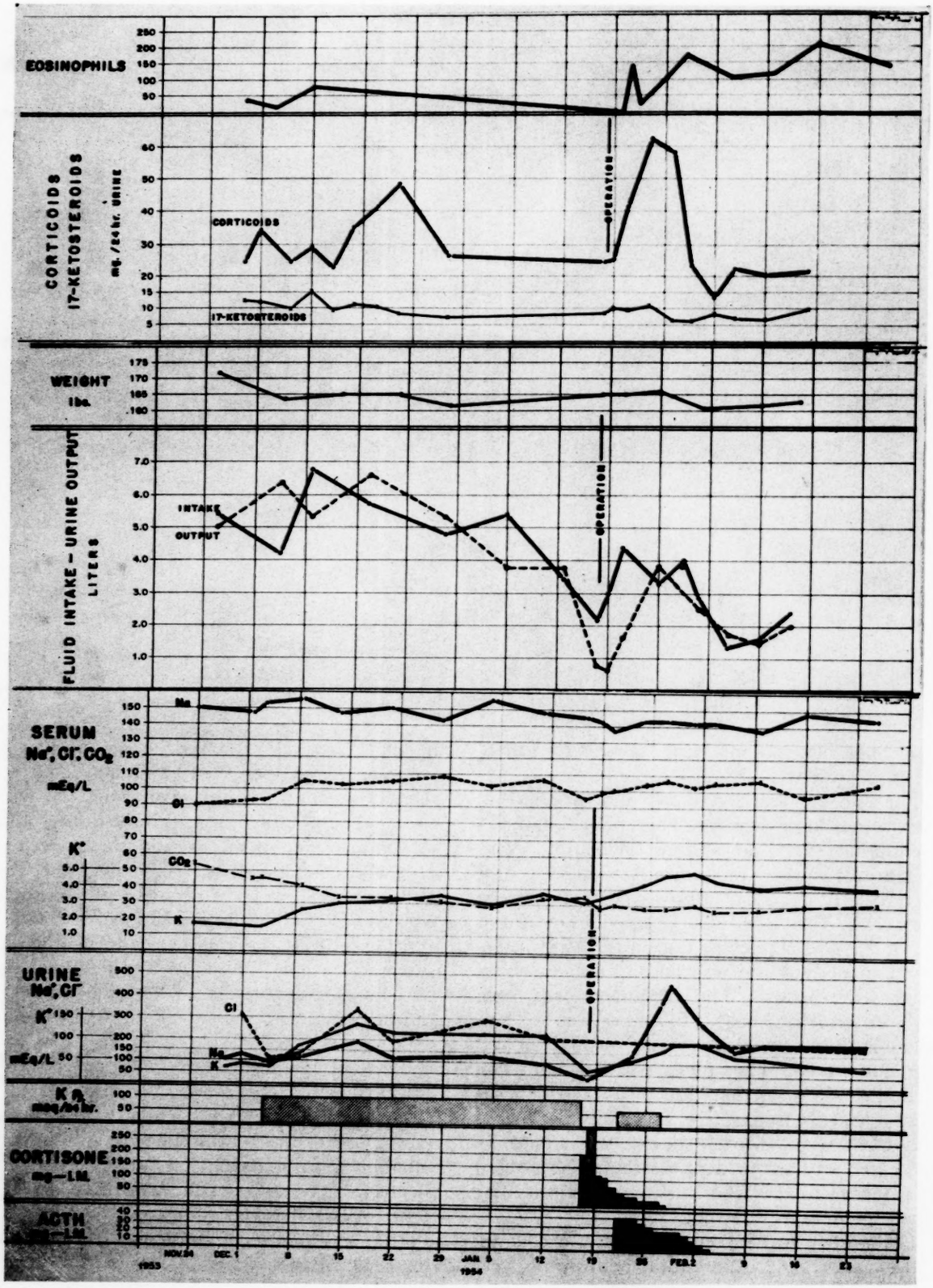
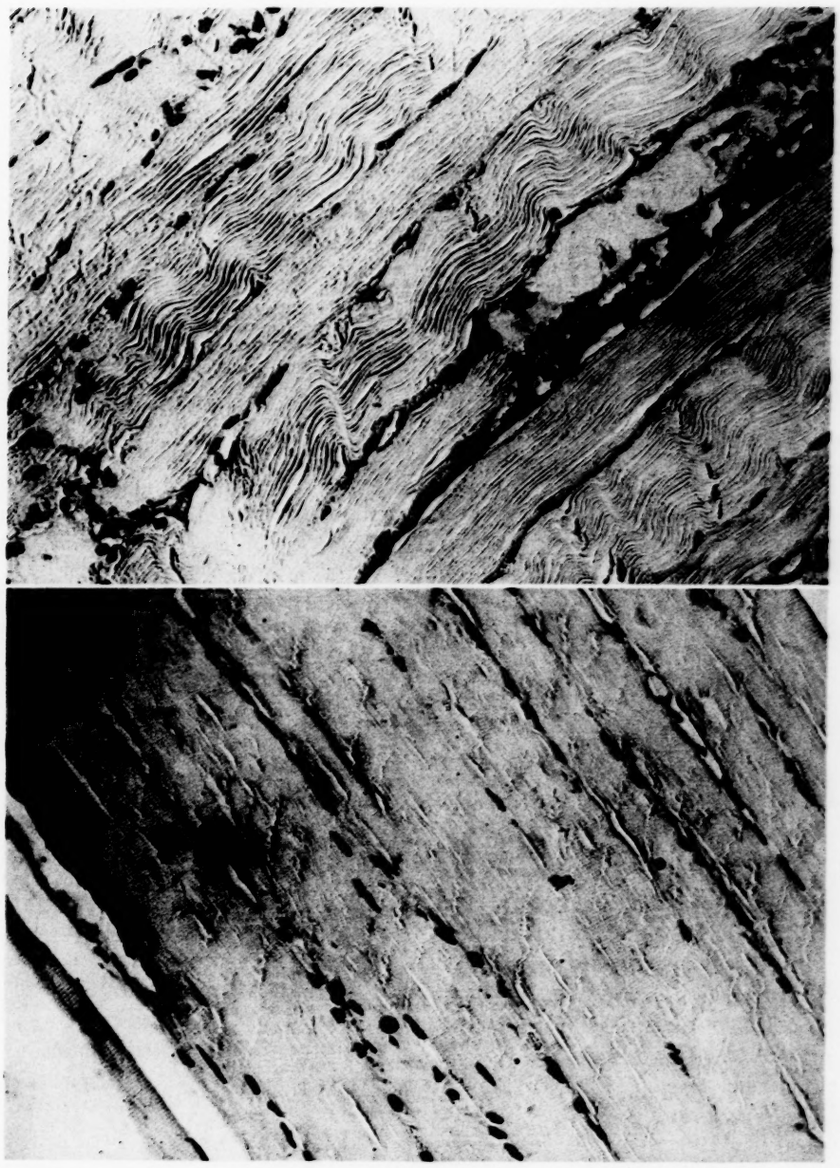


FIG. 2. Summary of observations preceding and immediately following removal of the right adrenal tumor.



3A

3B

FIG. 3. Sections of biceps muscle. A, on entry before potassium replacement; note degenerative changes with some loss of cross-striations and cellular infiltration. B, after potassium replacement showing normal muscle.

pyelograms showed a normally functioning upper urinary tract with no evidence of renal displacement. X-rays did not reveal any evidence of osteoporosis. An electrocardiogram revealed low T waves in V_4 through V_6 with depression of the ST segment and U waves in V_2 through V_5 and was thought to be compatible with left ventricular hypertrophy. Urinary 17-ketosteroid studies were repeatedly normal, ranging from 6 to 15 mg. per twenty-four hours. Urinary corticoid excretions were constantly elevated, the values being 25 to 60 mg. per twenty-four hours (Norymberski method: normal range, 9.6 to 19.2 mg. per twenty-four hours). (Fig. 2.) An electroencephalogram was reported as being mildly, non-focally abnormal. The blood volume was 83 cc. per kg. (normal, 66 cc. per kg.). Biopsy of the biceps muscle revealed swollen fibers showing fatty infiltration and chronic inflammation. (Fig. 3A.)

The fluid intake and urine output ranged between 5 and 7 L. daily and were not influenced by pitressin intravenously or subcutaneously. The urine output responded immediately to restriction of the fluid intake with a resulting severe thirst.

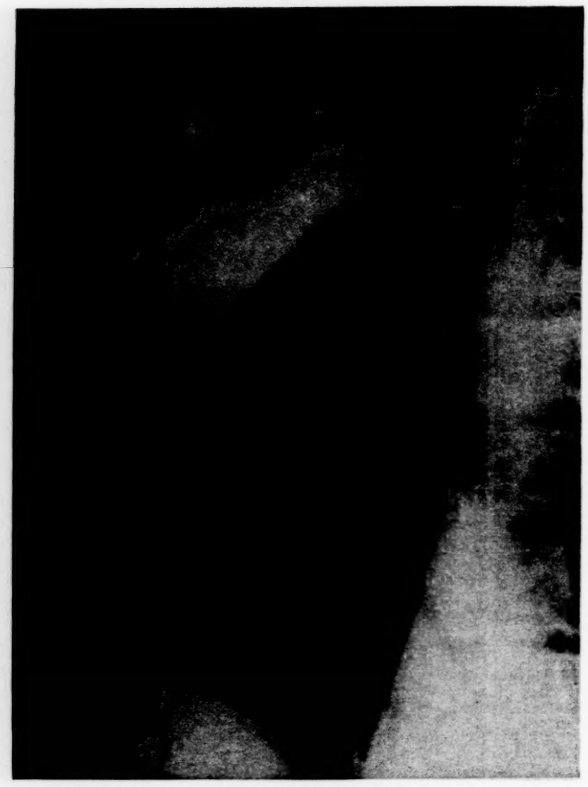


FIG. 4. Retroperitoneal air study showing tumor mass occupying area of right adrenal gland.

On December 3, 1953, the patient was started on a regimen of oral potassium chloride, 100 mEq. daily, with immediate and marked improvement in his thirst, weakness and abnormal reflexes. This therapy had no effect on the fluid intake and output, the patient's weight, the steroid excretion, or the fasting blood sugar. The serum sodium decreased to 145 mEq./L.; the serum potassium increased to 4 mEq./L.; the chlorides increased to 105 mEq./L.; and the CO_2 decreased to 30 mEq./L. The urinary excretion of potassium rose from 30 mEq. per twenty-four hours to approximately 100 mEq. per twenty-four hours. The electrocardiogram showed return of the T wave and ST segment changes to normal and considerable decrease in the size of the U waves. The arterial oxygen saturation increased to 91 per cent and the venous oxygen saturation decreased to 57 per cent.

On January 4, 1954, a retroperitoneal air study showed a right suprarenal, triangular mass which was thought to represent an adrenal tumor. (Fig. 4.)

On January 18, 1954, bilateral adrenal exploration by the lumbar route was performed.

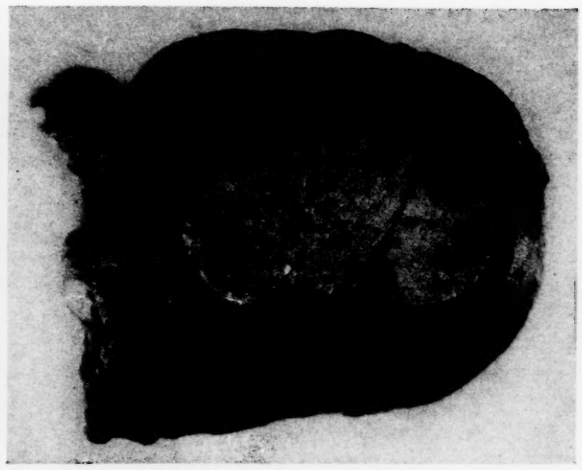


FIG. 5. Adrenal tumor. The cut section was of a canary yellow color.

The left adrenal was found to be normal in size and appearance. However, there was a 4 cm. mass replacing the right adrenal gland which was completely removed. (Fig. 5.) On section this tumor was canary yellow and there was a normal medulla and a small amount of residual cortex tissue. This tumor consisted of three distinct cellular patterns. (Fig. 6.) The patient did very well following surgery and his thirst, strength, fluid intake and output, serum electrolytes, fasting eosinophil count, blood volume, muscle biopsy (Fig. 3B) and electroencephalogram returned to normal. The urine 17-ketosteroids remained normal and the urinary corticoids dropped to a level of 20 mg. per twenty-four hours. The U waves disappeared from the electrocardiogram. The patient was discharged without medications on February 27, 1954.

The patient was readmitted on April 17, 1954, because of return of his thirst, polyuria and polydipsia over the previous ten days. Physical examination revealed a blood pressure of 172/128, pulse 82 per minute, temperature 98.4°F. The liver was 3 cm. below the right costal margin and slightly tender. The neurologic examination was normal. Physical findings were otherwise unchanged since his previous entry. Repeat hemogram, urinalysis, fasting blood sugar and x-rays of the chest and skull were normal. Serum potassium was 2.0 mEq./L.; sodium, 165 mEq./L.; chlorides, 96 mEq./L.; and CO_2, 45 mEq./L. The electrocardiogram at this time showed high U waves and the electroencephalogram again was diffusely abnormal. Excretion of 17-ketosteroid, which was

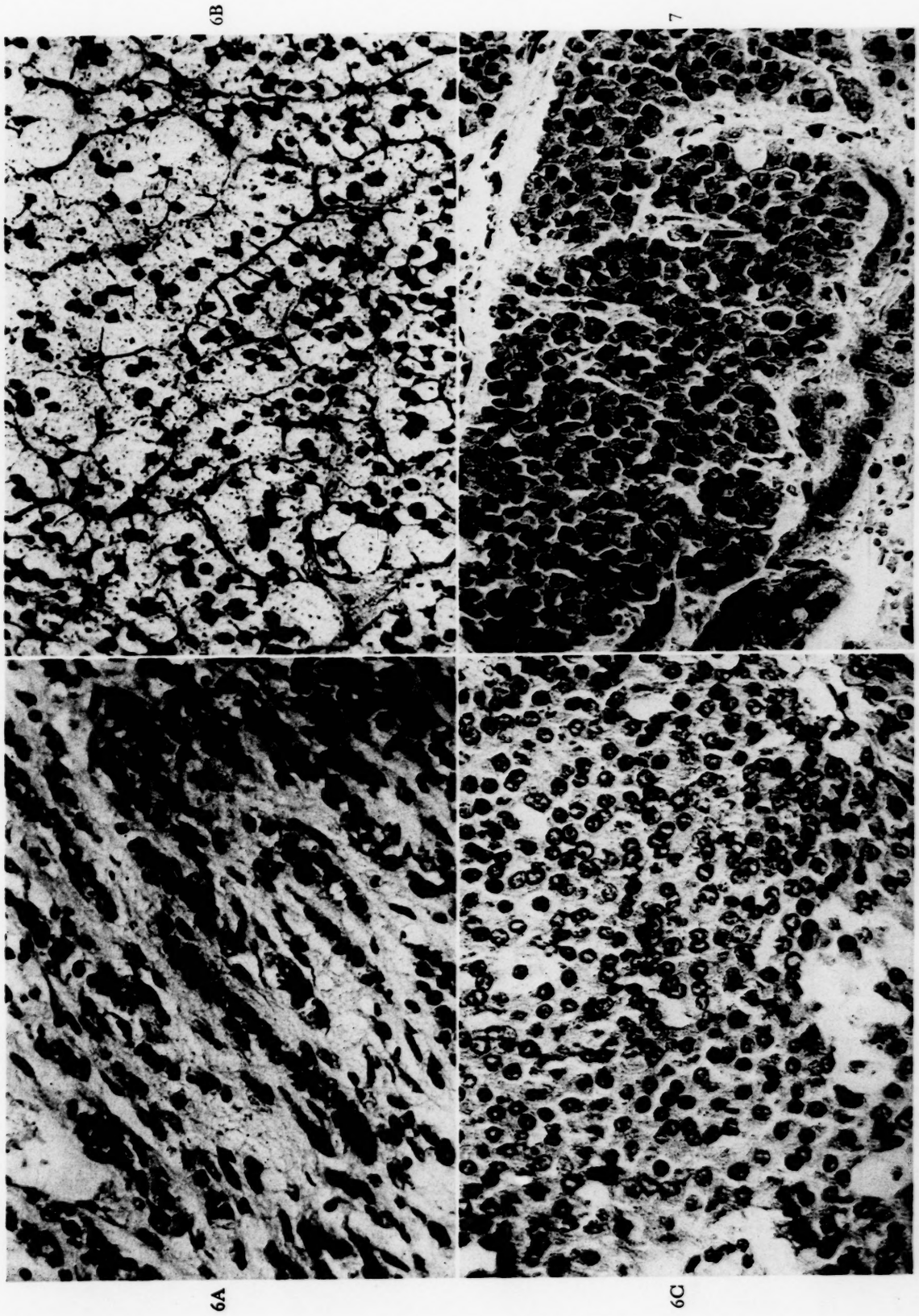


FIG. 6A to C. Sections of the adrenal tumor showing the three predominant cell types which were later found in the metastases examined at autopsy.
FIG. 7. Section of metastasis in the liver (autopsy specimen).

normal initially, rose terminally to the markedly abnormal value of 278 mg. per twenty-four hours and the urinary corticoid excretion rose to 31 mg. per twenty-four hours (Porter-Silber method: normal, less than 1 mg. per twenty-four hours). The fluid intake and output ranged from 2 to 5 L. per twenty-four hours. Fasting eosinophil counts showed a decrease from initially normal values to levels of five to twelve cells per cu. mm. A twenty-four-hour urine specimen was analyzed* for aldosterone content.[8] The resulting value was 12 μg. per 100 minutes (normal 4.8 per 100 minutes), DCA equivalent.

The patient was again started on treatment with potassium chloride supplements, with moderate improvement in his symptomatology and a return to normal of the T and U wave changes present on the electrocardiogram. However, his condition rapidly deteriorated and, on August 15, 1954, masses were felt in the liver for the first time and a x-ray of the chest demonstrated a markedly elevated right diaphragm. Five days later the patient died. Autopsy examination revealed a huge right retroperitoneal tumor mass with numerous metastases to the liver (Fig. 7), lungs and bone marrow. The left adrenal gland was approximately half the normal size. The metastases histologically resembled the cell types present in the original right adrenal tumor.

COMMENTS

This case of adrenal cortical carcinoma is unusual in several respects.

1. The patient on entry had symptoms of severe hypokalemia and clinical findings attributable to an excess of mineralocorticoid activity. At no time did the patient demonstrate the "cushingoid" facies or fat distribution, striae, increased venous pressure, generalized edema or impaired carbohydrate metabolism. To our knowledge a case of adrenal tumor producing an isolated mineralocorticoid excess has not been previously reported.

2. The severity of the hypokalemia was such that the patient was incapacitated by muscular weakness; reflexes were nearly absent; muscle biopsy showed degenerative changes; electrocardiogram showed U waves and ST-T wave changes; electroencephalogram was diffusely abnormal and the arterial oxygen saturation was markedly decreased as was the arteriovenous oxygen difference. All of these findings reverted to normal upon the institution of oral potassium chloride replacement therapy.

The disappearance of the electrocardiographic ST-T abnormalities upon repair of the potassium deficit was quite unexpected since these abnormalities had been attributed to the left ventricular hypertrophy which clinically persisted. However, these electrocardiographic findings reappeared during the patient's relapse and again disappeared promptly when potassium supplements were again administered. (Fig. 8.)

The diffuse electroencephalographic abnormality consisted of the presence of regular, slow 7 to 7½ CPS waves. The electroencephalogram became normal with potassium replacement but upon relapse it again became diffusely although mildly abnormal. (Fig. 9.) This record was characterized by irregular, slow activity which is probably characteristic of a more severe metabolic defect than the original electroencephalogram. These changes have been reported in untreated cases of Addison's disease or in Addison's disease treated only with DOCA.[1]

The increase in the arterial oxygen saturation (from 87 to 91 per cent) and the arteriovenous oxygen difference (from 7.5 to 34.0 per cent) with potassium replacement suggests that the degree of potassium deficit interfered with the ability of hemoglobin to take up oxygen at the lungs and to release it to the tissues. One of us (T. F.) has since produced severe hypokalemia in normal dogs and found a similar decrease in arterial oxygen saturation and A-V oxygen difference which was corrected by potassium replacement.

It is also of interest that during the severe hypokalemia a biceps muscle biopsy revealed muscle cell degeneration and lymphocytic infiltration, whereas after potassium replacement a biopsy from the same muscle was normal.

We postulate that the abnormalities described are due to hypokalemia, which in turn causes intracellular acidosis and thereby interference with oxygen utilization. The resultant tissue hypoxia readily explains all the abnormalities that were corrected by potassium replacement in this patient.

3. Diabetes insipidus was among the diagnoses initially considered in this case. However, the severe electrolyte abnormalities and the failure of the constant polyuria to respond to pitressin, either intravenously or subcutaneously, rapidly eliminated this diagnosis as a possibil-

* Performed by Dr. John Luetscher.

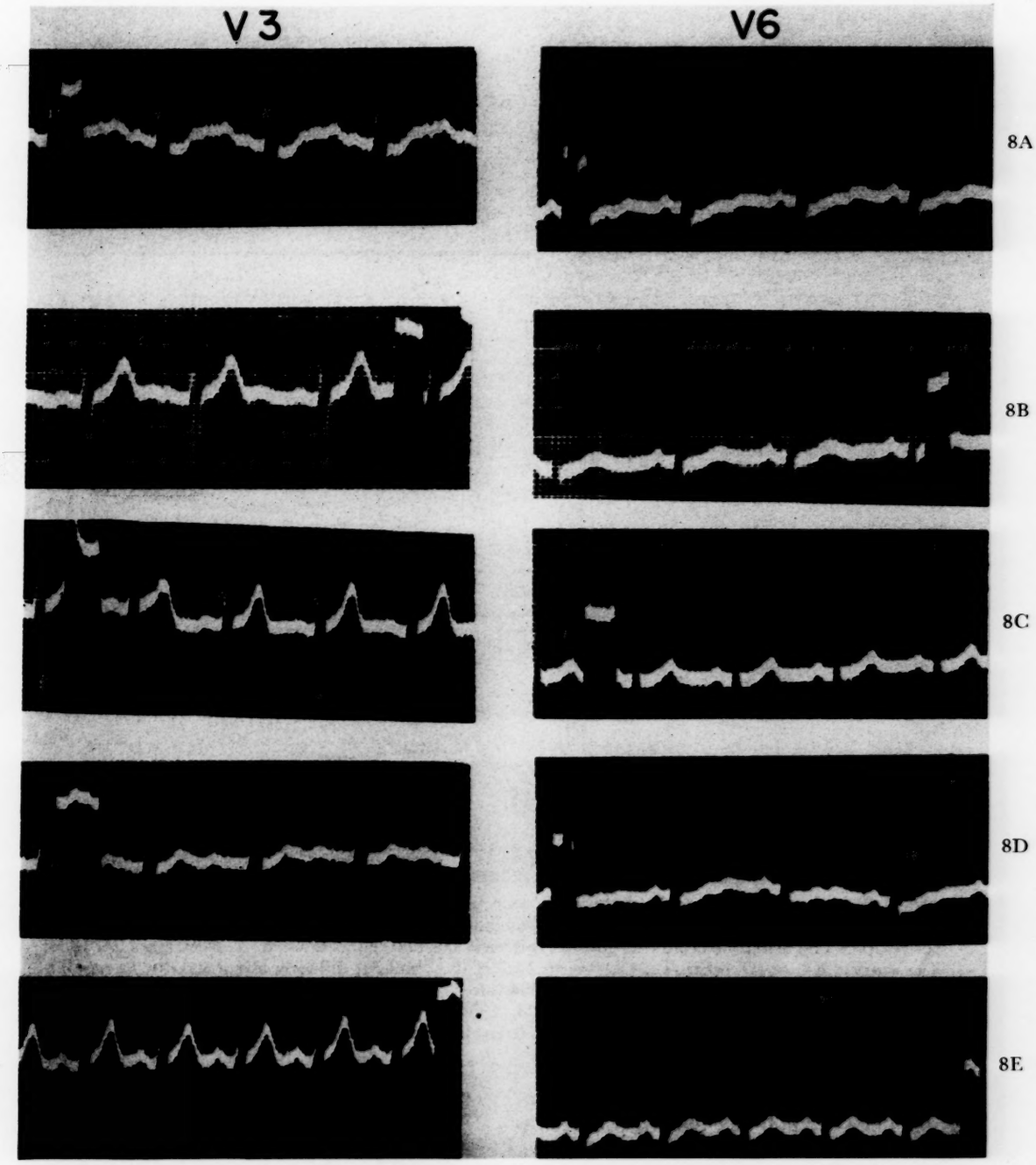


FIG. 8. Leads V3 and V6 showing the alterations in the ST segment, T wave and U wave with varying serum potassium levels. A, November 23, 1953 (on entry): K^+ = 1.8 mEq./L.; CO_2 = 53.0 mEq./L. B, December 18, 1953 (potassium replacement): K^+ = 3.0 mEq./L.; CO_2 = 33.4 mEq./L. C, February 5, 1954 (after tumor removal): K^+ = 4.3 mEq./L.; CO_2 = 28.1 mEq./L. D, April 20, 1954 (relapse): K^+ = 2.3 mEq./L.; CO_2 = 46.4 mEq./L. E, August 6, 1954 (potassium replacement): K^+ = 5.4 mEq./L.; CO_2 = 30.4 mEq./L.

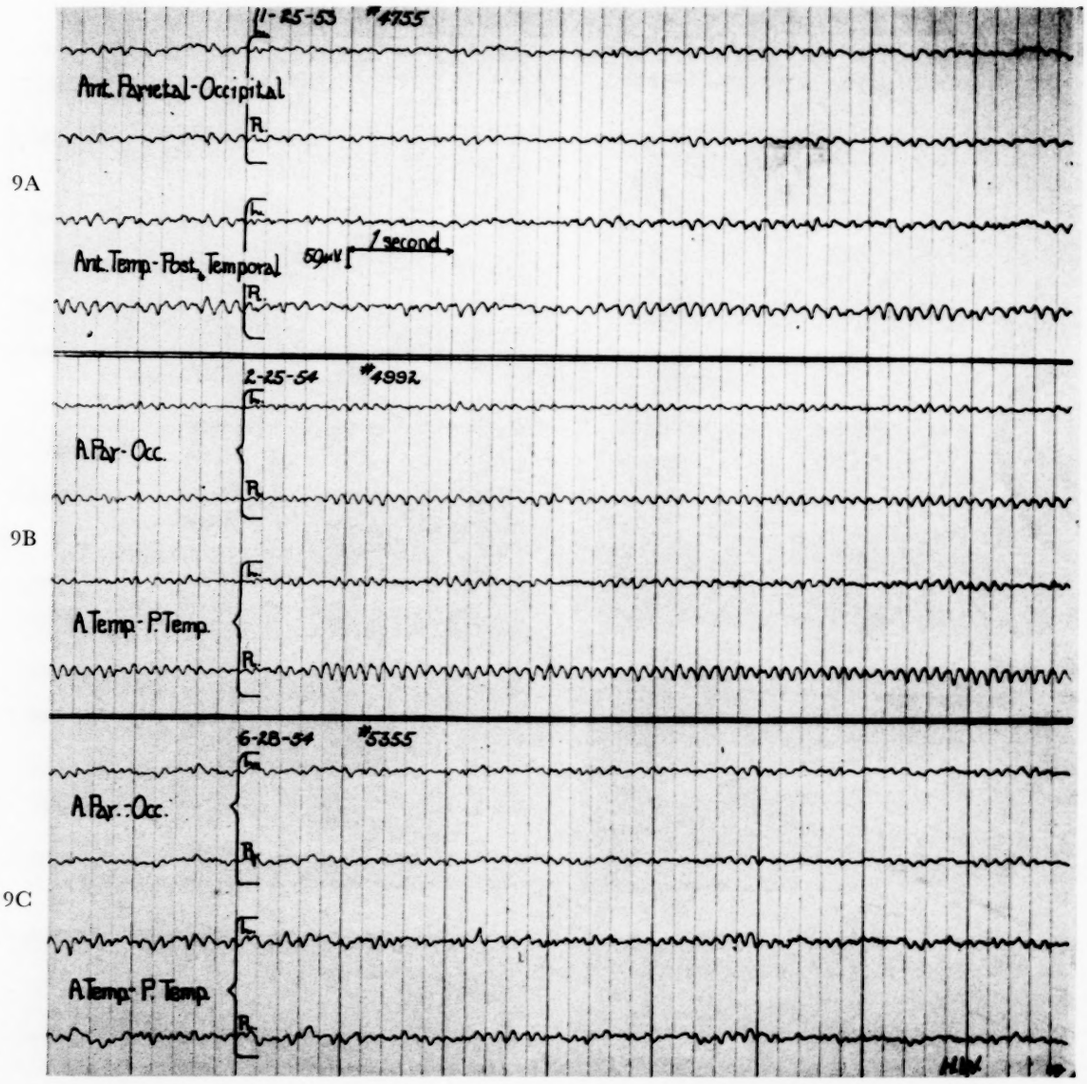


FIG. 9. Representative segments of the electroencephalograms taken at different phases of the patient's illness. The record of June 28, 1954, was made after potassium therapy had been instituted for relapse. The urinary steroid excretion at this time was markedly elevated. A, November 25, 1953 (on entry): K^+ = 1.7 mEq./L.; CO_2 = 46.2 mEq./L.; "mildly, diffusely abnormal due to regular slow, 7–7½ CPS waves." B, February 25, 1954 (after tumor removal): K^+ = 3.7 mEq./L.; CO_2 = 30.9 mEq./L.; "normal EEG." C, June 28, 1954 (relapse): K^+ = 3.9 mEq./L.; CO_2 = 33.3 mEq./L.; "mildly, diffusely abnormal due to irregular, slow, 6–7 CPS waves."

ity. The 5 to 7 L. urine output dropped immediately to below 2,000 cc. when water was withheld, although this resulted in severe thirst. We believed that the polyuria was secondary to the severe thirst and resultant polydipsia caused by the marked hypernatremia. The hypernatremia, thirst and polydipsia improved somewhat on potassium replacement and returned completely to normal upon removal of the adrenal tumor. A "diabetes insipidus-like" syndrome characterized by thirst, polydipsia, polyuria, sodium retention and potassium loss has been produced in normal dogs by the administration of DOCA.[9]

4. Throughout the initial phase of the patient's illness and for three months after his adrenalectomy the urinary 17-ketosteroid excretion remained normal. Then coincident with the onset of his gradual decline the excretion values began to rise, terminally reaching the value of 278 mg. per twenty-four hours. Throughout his course the urinary corticoids

were elevated and returned to normal levels only during the three months following adrenalectomy. Thereafter they rose to markedly abnormal levels. During this latter period urinary aldosterone assays were also elevated. Since aldosterone is not measured in the 17-ketosteroid or corticoid tests, and since there was no evidence in this patient of any effects not attributable to mineralocorticoid activity, we are unable to explain the source of these urinary steroids.

SUMMARY

A case of carcinoma of the adrenal cortex producing solely mineralocorticoid effect is presented and some of the manifestations briefly discussed. The abnormalities produced by the resulting severe hypokalemia seem of special interest and suggest impairment of oxygen transport and utilization, with interference with cerebral, myocardial and muscle metabolism.

Acknowledgments: Many people contributed to the study of this case. Our special thanks to Dr. Forrest M. Willett, Dr. Robert Fischer and Dr. Peter Lewis for their assistance and advice, to Miss Barbara Chapman for the steroid analyses, and to Miss Kay Hyde for the preparation of the charts.

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Spontaneous Hypopotassemia, Hypomagnesemia, Alkalosis and Tetany due to Hypersecretion of Corticosterone-like Mineralocorticoid*

IVAN J. MADER, M.D., *and* LLOYD T. ISERI, M.D.
Detroit, Michigan

ABNORMALITIES of electrolyte metabolism in classic forms of Cushing's syndrome, with concomitant disturbances of carbohydrate and protein metabolism, are well known and are explainable by excessive secretion of adrenal cortical hormones.[1–4] No case, however, has been reported in which the disorder has been limited to the electrolyte metabolism. The present study describes a case of spontaneous hypopotassemia, hypomagnesemia, alkalosis and tetany due to hypersecretion of corticosterone-like or aldosterone-like mineral corticoids.†

CASE REPORT

R. G. (27817), a thirty-three year old Negro woman, was admitted to Detroit Receiving Hospital on January 24, 1954, because of painful tetanic contractions of her hands of one day's duration. For approximately two months before admission the patient had noticed muscle weakness, pain and cramps, together with numbness of the extremities, restlessness and nervousness. Six months previously, during the fourth month of pregnancy, she had noticed intermittent spasms of her hands. There was no history of vomiting, diarrhea or ingestion of any medications except occasional salicylate compounds for headaches. She had had mild hypertension for five years and periodic frontal headaches for ten years. Twelve weeks prior to admission mild pre-eclamptic toxemia of pregnancy had developed but the patient delivered a normal fetus three weeks later at another hospital. During the confinement, prior to delivery, the patient was slightly edematous and the blood pressure was elevated to 170/108 mm. mercury. The plasma sodium was 131 mEq./L., potassium 3.35 mEq./L., chloride 94.5 mEq./L., CO_2 combining power 53.2 vol. per cent, serum uric acid 7.0 mg. per cent, and blood non-protein nitrogen 26 mg. per cent. Shortly after delivery, bilateral tubal ligation was performed.

Physical examination revealed a well developed and well nourished patient, acutely ill with obvious tetany. A grade 2 hypertensive retinopathy was present. A positive Chvostek sign was elicited. The heart was slightly enlarged and the blood pressure was 170 mm. Hg systolic and 90 mm. Hg diastolic. No masses or organs were palpable in the abdomen. There was no evidence of Cushing's syndrome or adrenogenital syndrome.

Tetany was readily relieved by rebreathing her own expired air from a paper bag, but the Trousseau sign remained positive. Biochemical studies, summarized in Table 1, showed the presence of hypopotassemic alkalosis with plasma potassium concentration of 1.6, sodium 143, chloride 84, and CO_2 content of 42 mEq./L. The serum calcium was 4.25 mEq./L. by a standard chemical method and 3.95 mEq./L. by the spectrographic method.[5] The serum magnesium was 1.1 mEq./L. and inorganic phosphorus 2.7 mg. per cent. The arterial blood

† Dr. Jerome W. Conn, in his presidential address at the 27th Annual Meeting of the Central Society for Clinical Research, described a case identical with the case presented here, and called it "primary aldosteronism."

* From the Departments of Medicine, City of Detroit Receiving Hospital and Wayne University College of Medicine, Detroit, Michigan. Presented before the 27th Annual Meeting of the Central Society for Clinical Research, Chicago, Illinois, October 29, 1954. Supported in part by grants from the National Institute of Health, the American Heart Association and the Michigan Heart Association.

H was 7.5 and the derived pCO_2 was 56 mm. Hg. The blood urea nitrogen was 13 mg. per cent and the fasting blood sugar on the second day was 76 mg. per cent. Serum albumin was 4.4 and globulin 2.3 gm. per cent.

The initial urinalysis (uncatheterized specimen) show a specific gravity of 1.014, albumin 2 plus, sugar 1 plus, acetone 4 plus, and white blood cells of 15 to 18 per high power field. Catheterized urine on the following day showed a trace of albumin, no sugar, no cellular elements and specific gravity of 1.004. The blood hemoglobin was 12.4 gm. per 100 ml., white blood count 10,500 per cu. mm., with 71 per cent neutrophils, 15 per cent lymphocytes, 9 per cent monocytes and 5 per cent eosinophils. The total eosinophil count was 283 per cu. mm. The phenolsulfonphthalein excretion was 25 per cent in twenty minutes. The electrocardiogram revealed flat to inverted T waves, prominent U waves, and prolonged S-T segment, indicative of hypopotassemia and hypocalcemia. Intravenous pyelographic studies were normal. Presacral air insufflation studies were also normal.

TABLE 1
BIOCHEMICAL STUDIES BEFORE AND AFTER TWENTY-ONE DAYS OF INTERMITTENT POTASSIUM CHLORIDE THERAPY*

Blood and Urine Values	Initial	After Treatment
Plasma Na (mEq./L.)	143	150
Plasma K (mEq./L.)	1.6	3.7
Plasma Cl (mEq./L.)	84	101
Plasma CO_2 (mEq./L.)	42	28
Serum Ca (mEq./L.)	4.25	4.75
Serum Mg (mEq./L.)	1.12	.....
Serum P (mg.%)	2.7	2.6
Blood pH	7.5	.....
Blood pCO_2 (mm. Hg)	56	.....
Blood urea nitrogen (mg. %)	13	.....
Urine pH	6.5	.....

* 6 gm./day.

The patient was given 20 ml. of 10 per cent calcium gluconate intravenously without alleviating the positive Trousseau sign. Infusion of 40 mEq. of potassium chloride solution produced no change in the degree of muscle irritability.

After supplementary potassium chloride therapy of 80 mEq. per day, the plasma sodium was 150, potassium 3.7, chloride 101, and CO_2 content 28 mEq./L. Muscle irritability, as judged by the Trousseau sign, gradually disappeared and muscle strength improved markedly.

Further studies were carried out to determine the mechanism of these biochemical abnormalities.

METHODS

Complete metabolic balance studies for Na, K, Cl, Mg and N were conducted for thirty days following readmission on May 6, 1954. Intake was analyzed by a double tray technic, wherein a duplicate tray of food and leftovers of an identical tray served to the patient were analyzed separately. Three-day pooled samples were homogenized and aliquot samples were obtained for analysis. Stools and urines were also pooled and analyzed every three days. Calculation of intracellular balance was made by assuming extracellular confinement of chloride.[6,7] Corrections for nitrogen balance were not made because of its relative stability.

Serial specific renal function studies, using inulin[8] and para-amino hippurate clearances, were made with two to three ten-minute collections of urine.[9] On one occasion endogenous creatinine clearance $\times$ 0.9 was used to estimate the rate of glomerular filtration. Tubular reabsorption of water and electrolytes was calculated from clearances of inulin.

Urinary steroid excretion studies* were made on twenty-four-hour collections of urine, treated with ammonium sulfate, acidified to pH 2.0, and extracted four times (one minute each) with n-butanol (or 2:1 ether-ethanol mixture). Blue tetrazolium reducing chromogens were determined by a modification of the method of Chen, Wheeler and Tewell,[10] with incorporation of an internal standard in the analysis and thirty-minute color development. Phenylhydrazine reducing chromogens were determined by a modification of the Porter-Silber reaction,[11] carried out at room temperature with addition of an internal standard control in the procedure.

Bioassays of salt-retaining urinary corticoids were made according to the method described by Johnson, using log K/Na values.[12]†

Sodium and potassium were determined by

* These studies were undertaken by Dr. William Q. Wolfson of the Department of Medicine, Wayne University College of Medicine.

† The bioassay studies were conducted by Dr. Harry W. Hays of the Department of Physiology and Pharmacology, Wayne University College of Medicine.

means of the Beckman flame photometer, according to the method described previously.[13] Chloride was determined by the method of Schales and Schales[14] for plasma and urine, and Whitehorn[15] for stool and food. Serum and urine magnesium was determined by the Titan-

presence or absence of intrinsic organic renal disease, are depicted in Figure 1. Each of these studies was performed after withholding potassium chloride supplements for five to twenty days before the test. Thus at the time of each test there was an acute lowering of the plasma potassium

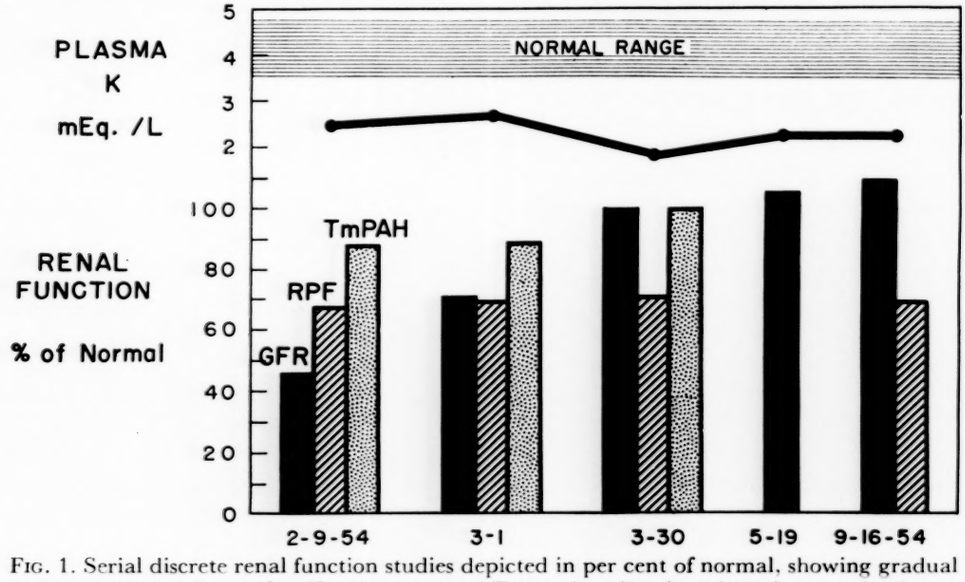

FIG. 1. Serial discrete renal function studies depicted in per cent of normal, showing gradual improvement in glomerular filtration rate and Tm_{PAH} in spite of persistently recurring hypopotassemia. Each study was carried out five to twenty days after temporary cessation of potassium chloride therapy.

yellow method, using starch colloid stabilizer.[16] Stool and food magnesium was determined in a similar manner after digestion with perchloric-nitric acid mixture. Nitrogen was analyzed by the macro-Kjeldahl method.

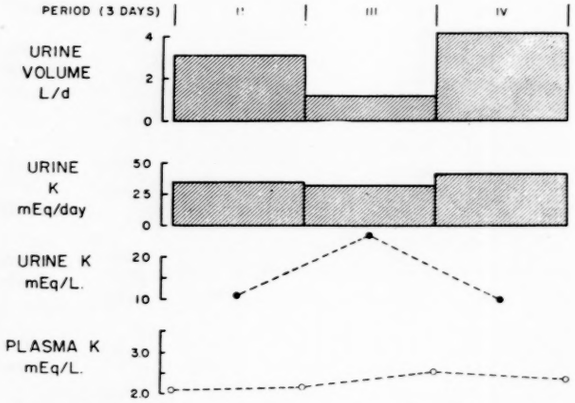

FIG. 2. Relationship of urinary volume to urine potassium excretion.

RESULTS

Renal Function Studies. Serial discrete renal function studies, carried out to determine the

to subnormal levels. The initial study on February 9, 1954, revealed a markedly depressed glomerular filtration rate (GFR 55.5 ml./min.), a moderately depressed effective renal plasma flow (RPF 445 ml./min.), and a slightly decreased maximal capacity of the tubules to excrete para-amino hippurate (Tm_{PAH} 63.1 mg./min.). Within three months both GFR and Tm_{PAH} were normal, but RPF remained low at 70 per cent of normal.

Since the patient showed a moderate degree of polyuria, it was necessary to determine whether or not this was a factor in the development of hypopotassemia. Figure 2 illustrates the relationship of urine volume to urine potassium concentration and potassium excretion, determined during a metabolic balance study on a 50 mEq./day potassium diet. Sharp reduction of urine volume from 3.05 L. per day to 1.20 L. per day by restriction of fluid intake resulted in a sharp rise in the urinary potassium concentration from 11.9 to 25.5 mEq./L. The specific gravity of the urine rose from 1.003 to 1.010. With unrestricted fluid intake and a consequent rise in urine volume, the urinary concentration

of potassium again decreased and the specific gravity fell to 1.002. The total quantity of K excreted into the urine varied very little with changes in urinary volume. (Excretion of magnesium was also independent of urinary volume.)

plasma potassium levels and a control twenty-four-hour urine were obtained. (Table II.) The patient was then given 80 mEq. of KCl supplements per day for eight days. Urine collections were obtained daily for the first two days and three-day pooled urines were obtained during

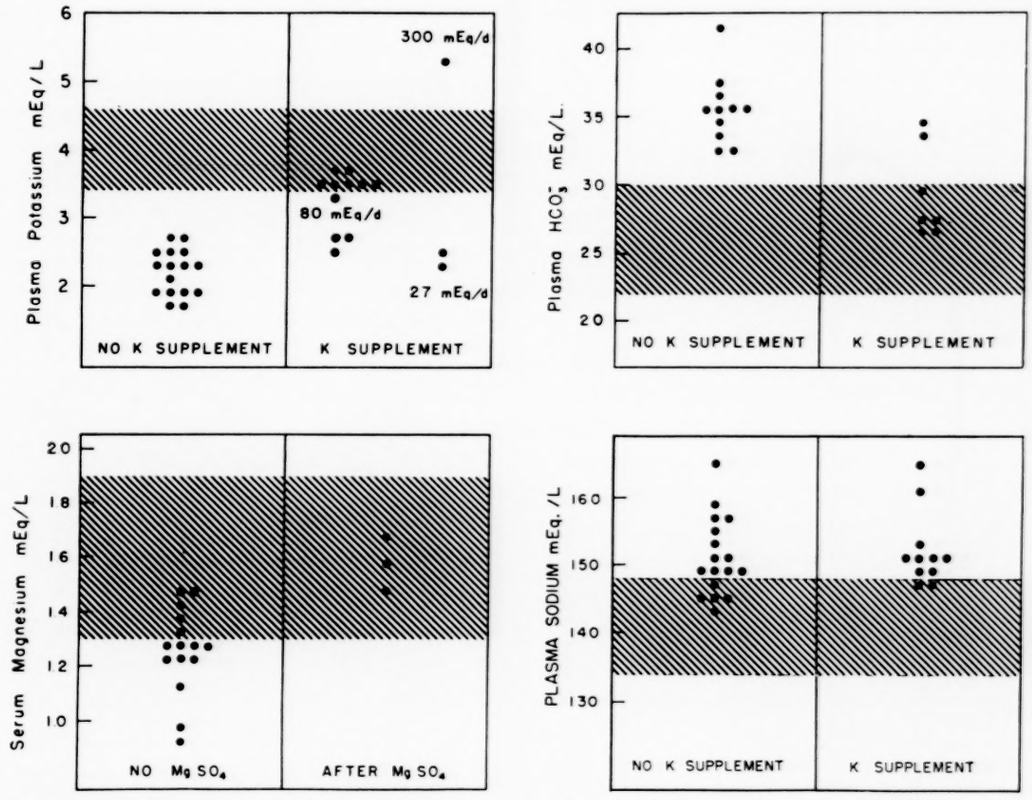

FIG. 3. Plasma potassium, sodium and bicarbonate levels before and afterpotas sium supplements, and serum magnesium levels before and after magnesium supplements.

Studies on Potassium Metabolism. During the ten-month period of observation potassium chloride supplements were given intermittently and plasma potassium levels were determined serially. (Figure 3.) When K supplements were withheld, the plasma level fell to values between 1.8 and 2.8 mEq./L. On several occasions a fall to subnormal levels occurred within five days after cessation of therapy. With 80 mEq. of potassium chloride supplements per day, low normal levels were usually obtained, but occasionally during outpatient visits subnormal values were observed. Supplements of 250 mEq. per day for six days raised the plasma potassium level to 5.3 mEq./L. and supplements of 72 mEq. per day had no effect on the plasma level.

Immediately upon initial admission to the hospital, the patient was given a diet calculated to provide 60 mEq. K^+ per day. Two control

the next twelve days. The diet and stools were not analyzed in this phase of the study.

The initial urine contained only 3.34 mEq. of potassium per liter and the urine/plasma potassium concentration ratio was 1.86. On the following day, with institution of potassium supplements, the urinary concentration was still only 6.28 mEq./L., with a U/P ratio of 2.50. Thereafter, a potassium U/P ratio less than 4.1 was never observed.

Estimating approximately 20 mEq. of K in the stool per day, there was a positive balance of some 55 mEq. of K per day during the eight days of KCl therapy and a negative balance of about 15 mEq. per day during the six days without therapy. The plasma potassium concentration rose from 1.8 to 3.7 mEq./L. with therapy and fell again to 2.7 mEq./L. after cessation of treatment.

Sodium diuresis occurred with potassium therapy. This was most marked at the onset of treatment and much less after five days.

A more precise metabolic balance study, including analyses of stool and food, was conducted four months later. (Table III, Fig. 4.)

TABLE II
EFFECT OF SUPPLEMENTARY KCL THERAPY DURING INITIAL ADMISSION ON URINARY ELECTROLYTE EXCRETION

Day	K Intake Supplement* (mEq.)	Urine				Plasma (mEq./L.)			
		Vol. (ml.)	K (mEq.)	Na (mEq.)	Cl (mEq.)	Na	K	Cl	CO_2
1	..	1,360	5	6	6	143	1.6	84	42
2	80	3,230	20	103	117	141	1.8	..	..
3	80	3,290	72	244	244	137	2.5	..	42
4	80	3,617	64	143	147	150	2.5	..	..
5	80	3,617	64	143	147	147	2.6	96	35
6	80	3,617	64	143	147	...	...	..	..
7	80	3,768	72	81	97	...	...	..	..
8	80	3,768	72	81	97	143	3.4	..	34
9	80	3,768	72	81	97	...	...	..	..
10	..	3,547	49	36	57	...	...	..	..
11	..	3,547	49	36	57	...	...	..	..
12	..	3,547	49	36	57	...	3.7	..	..
13	..	3,243	58	42	52	...	...	..	..
14	..	3,243	58	42	52	...	...	..	..
15	..	3,243	58	42	52	...	...	..	..
16	..	....	..	...	...	143	2.7	92	33

* Diet = 60 mEq./day.

Plasma potassium concentration remained subnormal all during the first four periods, each of three days, with an average potassium intake of 50 mEq. per day. Urinary and fecal excretion of potassium was exceedingly large at first, amounting to 98 per cent and 70 per cent of the intake, respectively, but gradually decreased with time. The extremely low stool K during period IV was undoubtedly due to a temporary delay in passage of stool, as indicated by the small quantity passed during this period and the large quantity during the following period.

As to total external exchange of potassium, negative balances of −82 and −18 mEq. were observed during the first two periods, equilibrium being established during the next two periods, even with persistent hypopotassemia. Total sodium balance was markedly positive (+213 mEq.), and chloride balance negative (−141 mEq.) during the first four periods of low potassium intake. Total magnesium balance was significantly negative (−51 mEq.) during the same interval.

Calculation of extracellular and intracellular changes (Table IV, Fig. 5) revealed an early minimal loss of intracellular potassium and

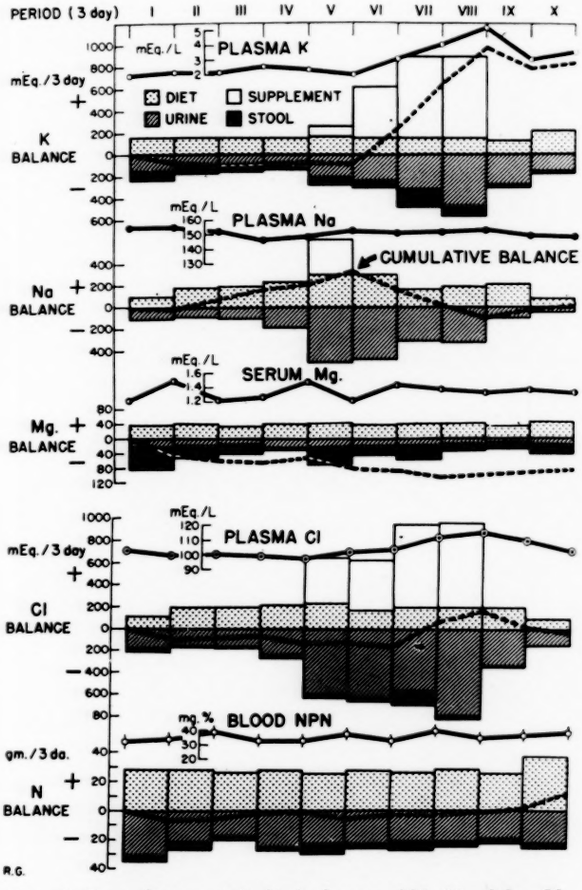

FIG. 4. Complete metabolic balance of K, Na, Mg, Cl, and N during low and high intake of potassium. Stool Na excretion was so small that graphic representation was not possible.

continuous gain of intracellular sodium during the period of low potassium intake. No consistent change in intracellular water content was observed, but a slight decrease in extracellular water was noted. Chloride loss was of the same magnitude as extracellular sodium loss and proportionately greater than extracellular water loss, reflecting the development of extracellular alkalosis.

Results of changes during period V are difficult to analyze because of the administration of parenteral KCl and NaCl.

During periods VI, VII and VIII potassium intake was increased to 200 and 300 mEq. per

TABLE III
METABOLIC DATA

Period (3 days)	Intake*							Urine						Stool						Plasma		Serum					Blood	Body Weight
	H_2O	Food	Na	K	Mg	Cl	N	Vol.	Na	K	Mg	Cl	N	Weight	Na	K	Mg	Cl	N	Na	K	Mg	Cl	CO_2	Ca	P	NPN	
	(ml.)	(gm.)	(mEq.)				(gm.)	(ml.)	(mEq.)				(gm.)	(gm.)	(mEq.)				(gm.)	(mEq./L.)		(mEq./L.)			(mg. %)		(mg. %)	(kg.)
I	7,005	3,290	102	154	40	117	28.6	9,955	112	148	22	188	30.2	636	7	88	64	27	5.6	155	1.9	1.2	104	34	10.2	2.9	32	75.1
II	4,880	4,400	187	156	41	196	28.0	9,160	89	110	19	168	21.2	629	8	64	33	15	5.8	155	2.2	1.5	100	.33	....	...	34	74.4
III	1,500	4,251	193	151	35	195	26.5	3,605	98	92	17	182	17.6	456	5	53	24	7	4.1	153	2.2	1.2	101	32	9.3	3.2	39	74.7
IV	10,340	4,410	240	147	41	216	27.7	12,545	188	126	24	260	25.1	152	2	7	5	19	1.7	147	2.5	1.3	99	36	....	...	33	74.6
V	9,950	4,400	299 (325)	168 (100)	42	223 (425)	25.4	12,998	491	206	22	462	22.6	934	15	69	44	30	7.5	147	2.4	1.5	98	35	10.7	3.7	32	74.8
VI	9,283	4,160	300	156 (468)	39	162 (468)	27.5	10,000	467	230	22	634	22.6	382	6	66	23	36	3.6	153	1.9	1.2	102	35	9.8	3.1	38	73.4
VII	7,641	4,140	167	147 (750)	39	191 (750)	26.9	9,160	299	310	21	570	20.7	1125	13	180	37	133	6.4	151	3.0	1.4	104	31	....	3.4	33	74.6
VIII	10,200	4,160	193	149 (750)	40	198 (750)	28.3	10,670	321	479	15	791	20.8	581	3	93	20	51	4.2	151	4.1	1.4	112	25	9.5	3.2	40	74.8
IX	5,347	3,810	210	125	34	203	25.4	7,620	117	278	13	351	19.2	336	2	33	17	5	3.9	151	5.3	1.3	115	28	10.3	3.3	35	74.7
X	8,143	5,784	82	224	47	94	37.1	8,230	57	147	19	148	22.3	306	2	23	27	4	4.5	149	3.0	1.3	111	26	9.7	3.0	37	73.5
End of x	.....	.....	.....	.....	..	.....	....	.....	...	...	..	...	....	....	..	...	...	...	...	148	3.5	1.3	103	30	10.0	3.1	39	74.1

* Numbers in parentheses indicate supplements.

day with oral supplements. As was to be expected, there was a sharp rise in plasma potassium concentration and a marked uptake by the cells, amounting to a total of 1,020 mEq. in nine days. Urine K output increased in step-like fashion but was not sufficient to prevent the continued rise of plasma K to supernormal levels.

Concomitant with potassium uptake, there was a markedly negative balance for sodium (−430 mEq.). During period VI both the extracellular and intracellular compartment contributed to this negative balance; however, during periods VII and VIII markedly negative intracellular sodium balance was accompanied by a positive extracellular balance. The extracellular volume decreased initially and then increased, whereas intracellular volume increased initially and then decreased later. Extracellular chloride gain was proportionately greater than extracellular sodium or water gain during periods VII and VIII, reflecting the correction of alkalosis and a rise in plasma chloride concentration.

With cessation of KCl therapy during period IX, a markedly negative K balance and a fall in plasma potassium level to subnormal levels occurred, due to the continued high urinary excretion of potassium. Intracellular sodium increased and extracellular volume decreased. During period X, with potassium intake of 72 mEq. per day, complete adjustment and equilibrium were noted.

TABLE IV
DERIVED BALANCE DATA

Period (3 days)	Total						Extracellular				Intracellular			
	Wt.	Na	K	Mg	Cl	N	H_2O	Na	K	Mg	H_2O	Na	K	Mg
	(kg.)	(mEq.)				(gm.)	(ml.)	(mEq.)			(ml.)	(mEq.)		
I	−0.7	− 17	− 82	−46	− 98	− 7.2	−0.55	− 83	+ 2	+2	−0.15	+ 66	− 83	−48
II	+0.3	+ 90	− 18	−11	+ 13	+ 1.0	+0.06	− 14	+ 0	−3	+0.24	+104	− 18	− 8
III	−0.1	+ 90	+ 6	− 6	+ 6	+ 4.8	+0.18	− 43	+ 5	+1	−0.28	+133	+ 1	− 7
IV	+0.2	+ 50	+ 15	+12	− 62	+ 0.9	−0.45	− 58	− 3	+2	+0.65	+109	+ 18	+10
V	−1.4	+118	− 7	−24	+ 8	− 4.7	−0.29	+ 10	− 5	−3	−1.11	+110	− 2	−21
VI	+1.2	−172	+328	− 6	− 40	+ 1.3	−0.65	−120	+10	+2	+1.85	− 52	+318	− 8
VII	+0.2	−145	+407	−19	+238	− 0.2	+1.43	+220	+16	+1	−1.23	−365	+391	−20
VIII	−0.1	−131	+327	+ 5	+105	+ 3.3	+0.57	+ 90	+16	0	−0.67	−221	+311	+ 5
IX	−1.2	+ 91	−186	+ 4	−153	+ 2.3	−0.86	−157	−29	−1	−0.34	+248	−157	+ 5
X	+0.6	+ 23	+ 54	+ 1	− 58	+10.3	+0.39	+ 30	+ 6	0	+0.21	− 7	+ 48	+ 1

Acute studies on urinary potassium excretion were made serially during a prolonged period of observation. (Fig. 6.) During the initial study (February 9, 1954), shortly after the first admission, filtration of potassium was markedly diminished due to the low glomerular filtration rate. Seventy-five per cent of filtered potassium was excreted and only 25 per cent reabsorbed by the tubules. With improvement in glomerular filtration to normal (March 30, 1954), the amount excreted into the urine decreased to 59 per cent of that filtered, 41 per cent being reabsorbed. Even after six months of normal GFR and Tm_{PAH} the amount of K reabsorbed was still only 68 per cent of the amount filtered.

During a sodium para-aminohippurate load (February 9, 1954), secretion of potassium by

the tubules was demonstrated, the amount excreted exceeding the amount filtered by 42 per cent. With improvement in glomerular filtration rate, sodium PAH load still produced an increase in potassium excretion, although this effect was less marked.

Studies on Alkalosis. A plasma carbon dioxide content of 42 mEq./L., initially found together with an arterial blood pH of 7.5, indicated a plasma CO_2 tension of 56 mm. of Hg, substantiating the presence of metabolic alkalosis. During the various periods of observation plasma CO_2 content was elevated when KCl supplements were not given and was usually, but not always, within the normal range when adequate supplements were administered. (Fig. 3.)

Development of alkalosis during potassium depletion was studied by analysis of the pH and titratable acidity of the urine. (Table v.) During the nine-day period of study on a 60 mEq. K/day diet, the plasma K fell from 3.5 to 2.5 mEq./L. and the plasma CO_2 content rose from 32 to 37 mEq./L. Urinary pH varied between the narrow range of 6.4 and 6.7 and the titratable acid varied in the subnormal range from 11.4 to 17.0 mEq. per day. Alkalosis thus appeared to develop in the presence of slightly acid urine, but with subnormal excretion of titratable acids.

Metabolic balance studies showed that during potassium therapy (VI, VII, VIII) potassium entered the cells (+1020 mEq.) and sodium left the cells (−637 mEq.) at a ratio of approximately 3:2. (Fig. 5.) Since the magnesium balance during this interval was only slightly negative (−23 mEq.), it might be postulated that approximately 360 mEq. of hydrogen ion emerged from the cells. Total extracellular bicarbonate content decreased by approximately only 40 mEq. during the period of high KCl therapy.

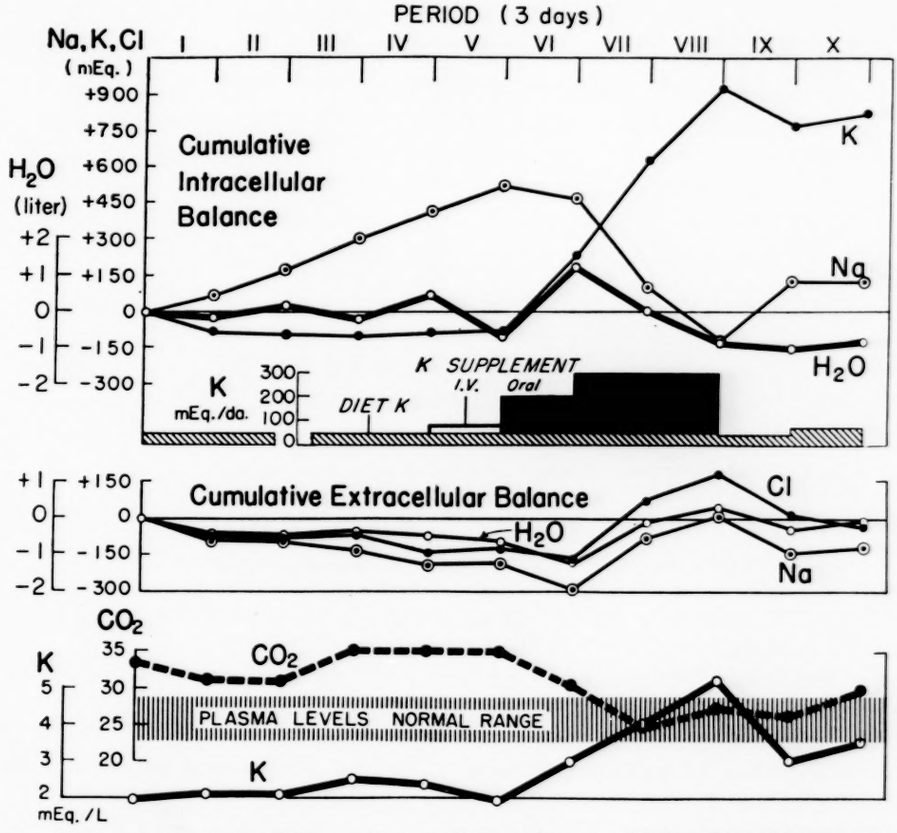

FIG. 5. Cumulative intracellular and extracellular balances of K, Na, Cl and H_2O, and plasma CO_2 and K concentrations during low and high intake of potassium.

Studies in Magnesium Metabolism. Serum magnesium levels, obtained periodically, were either low normal or, more frequently, subnormal. Magnesium sulfate supplements resulted in normal levels. (Fig. 3.)

Balance studies with magnesium intake of 12 to 14 mEq. per day showed a persistently

negative balance for twenty-one days, due mainly to large quantities of magnesium appearing in the stool. (Table III, Fig. 4.) Fecal loss was especially noticeable at the onset of the study and gradually decreased. The small amount of fecal magnesium and the apparent positive balance during period IV were due to temporary constipation, as evidenced by sudden release of magnesium in the stool during the following period. Positive balance was attained only after period VII, concomitant with replenishment of cellular potassium.

Acute urinary excretion of magnesium was studied after restoration of normal GFR and Tm_{PAH}, using clearance methods. (Fig. 7.) During the control period as much as 16 per cent of the amount filtered was excreted into the urine, 84 per cent being reabsorbed. Infusion of magnesium sulfate at the rate of 0.9 mEq. per minute resulted in rapid rise of serum magnesium levels and increase in the rate of excretion, due to increased filtration. The absolute quantity reabsorbed by the tubules remained relatively constant.

Studies Pertaining to Adrenal Cortical Activity. The tendency to retain sodium and to lose potassium suggested the possibility of some abnormality in adrenal cortical activity, even though clinical evidence of typical Cushing's syndrome or adrenogenital syndrome was lacking.

A glucose tolerance test after adequate carbohydrate intake for at least three days revealed a slight delay in return of the blood sugar to the control level. True fasting blood sugar was 67, one-half hour after ingestion of glucose—123, one hour—130, two hours—142, three hours—50, four hours—53 mg. per cent.

Analysis of thermal sweat showed the following values: Na 6.6, K 6.3, Cl 1.9, and Mg 0.5 mEq./L., indicating increased adrenal cortical activity.[17] Injection of desoxycorticosterone, however, failed to demonstrate a paradoxical increase in sodium excretion.

Results of the analysis of urinary steroids are given in Table VI.* Blue tetrazolium-reacting corticoids were increased significantly and the Porter-Silber (phenylhydrazine-reacting) corticoids were only slightly elevated above normal. The difference of these two fractions, representing the corticosterone-group of steroids was, therefore, significantly elevated. Likewise, the ratio of phenylhydrazine-reacting corticoids to

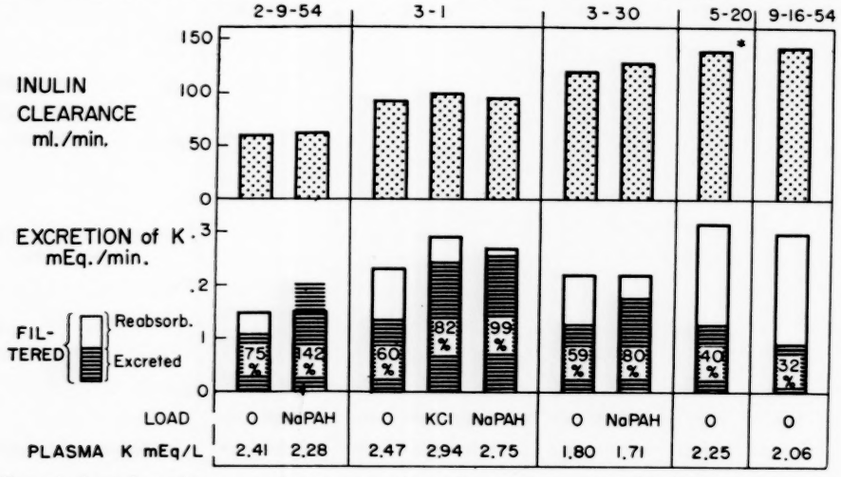

FIG. 6. Serial studies on urinary excretion of potassium. Asterisk indicates creatinine clearance × 0.9.

TABLE V

URINARY TITRATABLE ACID AND PH DURING DEVELOPMENT OF HYPOPOTASSEMIC ALKALOSIS

Date	Plasma (mEq./L.)		Urinary Titratable Acid (mEq./d.)	Urine (pH)
	K	CO_2		
Feb. 17	3.5	32	....	...
19	...	..	11.4	6.5
20	...	..	15.4	6.5
21	...	..	12.5	6.4
22	3.1	32	....	...
23	...	..	16.8	6.7
24	...	..	17.0	6.7
25	2.5	37	....	...
26	...	..	12.5	6.5

* The statement that derivatives of 17 hydroxycorticoids were increased, originally made in the abstract (*J. Lab. & Clin. Med.*, 44: 895, 1954), is an error, due to miscalculation of the data.

this difference was 0.56 or less, indicating a preponderance of corticosterone group of steroids in excess of the cortisone group of steroids. Excretion of 17-ketosteroid was normal, being fairly constant on three occasions, 6.6, 8.8 and 8.8 mg. per gm. creatinine. The Pettenkofer steroids were within normal limits.

above the normal and indicated excessive excretion of salt-retaining steroids.

COMMENTS

The fact that hypopotassemia could be demonstrated even after return of both glomerular filtration rate and capacity of the tubules to excrete para-aminohippurate to the normal range indicated that intrinsic renal disease probably was not responsible for continued potassium loss. Low GFR and Tm_{PAH}, originally present, were perhaps due to severe depletion of tissue potassium.[18] Hypopotassemia *per se* had very little effect on GFR or Tm_{PAH}, as indicated by insignificant changes induced by KCl loading and continued improvement, in spite of acute lowering of plasma potassium levels, just prior to each testing. Although possible, it seems unlikely that the mild toxemia of pregnancy, which occurred eleven weeks prior to the initial study, was responsible for the decreased GFR and Tm_{PAH}. The renal plasma flow, as measured by para-aminohippurate clearance, remained constantly subnormal and undoubtedly reflected the underlying vascular hypertension which the patient had had for at least five years.

The polyuria manifested by this patient was ruled out as the cause of potassium loss by control studies on urine volume. The patient became extremely restless during restriction of water intake, although no significant changes in the plasma electrolyte concentrations could be detected.

It was apparent from metabolic studies that there was a tendency toward loss of potassium in the stool and urine. The gradual decrease

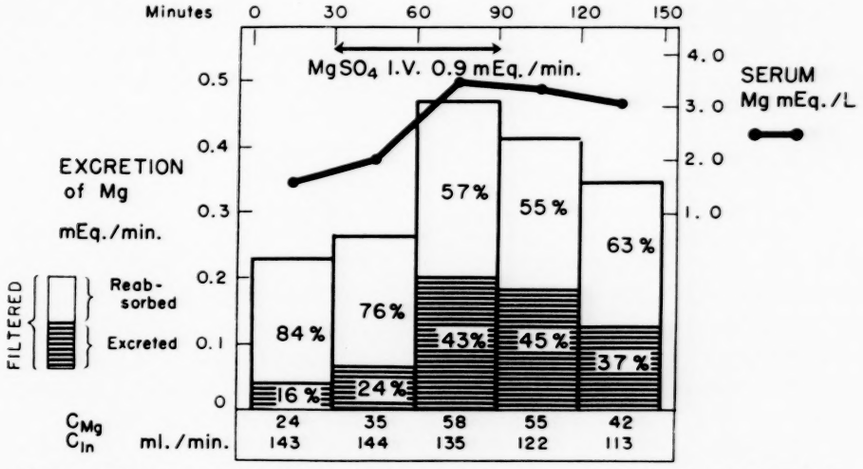

FIG. 7. Urinary excretion of magnesium before, during and after intravenous infusion of $MgSO_4$ at 0.9 mEq. per minute for sixty minutes.

Injection of 25 mg. of cortisone intravenously, complicated by a pyrogenic reaction, resulted in a marked eosinopenic response, from 280 to 40 per cu. mm.; a rise in urine volume, from 16 to 220 ml. per hour; a rise in urine Na concentration, from 13 to 78 mEq./L.; a rise in chloride, from 25 to 101 mEq./L.; and a slight rise in potassium, from 21 to 26 mEq./L. These changes suggested a paradoxic effect of exogenous cortisone given intravenously.

TABLE VI
URINARY CORTICOIDS*

	1–29	5–12	6–8	8–5
BTZ†	...	41.1	35.0	40.3
P-S‡	...	12.6	10.8	14.4
17 K-S§	6.6	....	8.8	8.8
BTZ minus P-S	...	28.5	24.2	25.9

* Expressed as mg. per gm. creatinine.
† Blue-tetrazolium reducing corticoids.
‡ Corticoids measured by Porter-Silber phenylhydrazine method.
§ Total 17-ketosteroids.

Bioassay of the urine obtained on two separate days, when KCl supplements had been discontinued, showed excretion of salt-retaining corticoids equivalent to 270 and 450 μg. DOCA per day. These values were definitely increased

in this tendency during the first four periods on minimal intake of potassium suggested either (1) a gradual decrease in the stimuli for elimination of potassium, possibly because of hospital confinement, or (2) a metabolic lag period from higher intake prior to the onset of the study. The latter possibility was unlikely in view of the marked delay of potassium balance in reaching an equilibrium and the estimated K intake of only 15 to 20 mEq. per day more in the home than in the metabolic diet.

An intake of 50 mEq. of K per day should have been adequate for positive balance and correction of hypopotassemia, in view of the rapid uptake of K observed in two cases of catharsis-induced hypopotassemia studied by Schwartz et al.[18] The fact that this patient failed to retain potassium and correct her hyperpotassemia on a 50 mEq. K diet implies a definite abnormality in potassium metabolism.

Renal loss of potassium may be attributed either to excessive secretion or decreased reabsorption by the tubules. The net quantity "reabsorbed" by the tubules was only 68 per cent of the amount filtered, even after GFR and Tm_{PAH} had become normal. This was distinctly below the normal of 80 per cent reported by Earle et al.[19]

Failure of the tubules to reabsorb K at a normal rate was apparently temporary, since immediately after the initial admission, when K depletion was undoubtedly the most severe, the urine-plasma potassium concentration ratio was as low as 1.8, a value usually not attained even in severe potassium depletion.[20]

Thus it appeared that some common factor was causing potassium loss from the bowels and the kidneys and that this factor had a self-limiting influence on tubular rejection (or excretion) of potassium.

Concomitant with the tendency toward potassium loss and hypopotassemia, there was a distinct tendency toward sodium retention. Random plasma sodium concentrations were usually but not always elevated above normal and metabolic studies showed retention of sodium during low K intake and loss of sodium during high K intake.

Calculations showed that these changes in sodium balance occurred primarily within the cells, affording an explanation for the absence of edema in the face of sodium retention. During K depletion and sodium retention, the extracellular fluid actually decreased; while during K repletion and sodium loss, the extracellular fluid increased, after a temporary unexplainable decrease for two to three days.

Development of alkalosis was undoubtedly related to potassium depletion[21,22] and since total titratable acids in the urine during potassium depletion were subnormal, extrarenal factors were probably at least partly responsible. Maintenance of an alkalotic state by persistent hypokaliemia must have been due to renal secretion of hydrogen ions.[23]

Metabolic studies revealed a large increment of fecal magnesium at the onset of hospitalization and a gradual decrease with confinement. Since the intake of magnesium was critically low (14 mEq./d.), the negative balance initially observed in this patient may have simply reflected an insufficient intake; however, the equilibrium attained during the last nine days of study (after increase of body potassium) suggested at least a temporary defect in magnesium metabolism.

Reabsorption of magnesium by renal tubules appeared to be somewhat impaired, as judged by the subnormal net reabsorption of filtered magnesium by the tubules. It would appear from data given by Heller et al.[24] that normally at least 95 per cent of the filtered magnesium is reabsorbed by the tubules. In the present case only 84 per cent was reabsorbed.

No symptoms could be ascribed to the hypomagnesemia *per se*, although the patient herself volunteered the information that headaches were alleviated by supplementary intake of magnesium. Muscular irritability, as judged by a positive Trousseau test, was apparently not caused by hypomagnesemia, since the test remained positive despite correction of the low serum magnesium level.

The entire picture of hypopotassemic alkalosis with retention of sodium, found in this patient, could be explained adequately by excessive secretion of adrenal corticoids; however, the absence of clinical features of Cushing's or adrenogenital syndromes suggested the possibility of oversecretion limited to the mineral corticoids. Chemical analysis of the urine indicated a preponderance of corticosterone or corticosterone-like hormones with unaltered or desoxy-17-carbon. Since corticosterone itself, when injected into rats, does not produce sodium retention,[12] it was most probable that the fraction found in the urine by chemical analysis and the salt-retaining component demonstrated by bioassay technic was not corticosterone but a corticosterone-like steroid

with unaltered 17-carbon. It is probable that this salt-retaining steroid was aldosterone.[25,26]

A case of hypopotassemia presumably due to excessive loss of potassium in chronic pyelonephritis has been reported by Cope and Garcia-Llaurado,[27] and Evans and Milne.[28] A significant amount of electrocortin (aldosterone), with salt-retaining activity, was isolated from the urine of this patient by paper chromatography.[27] It is possible that hypopotassemia developed in this patient and also perhaps in the patient reported by Earle et al.[19] as a result, in part, of oversecretion of salt-retaining, potassium-losing steroid. The renal dysfunction in these cases may have been secondary to severe chronic potassium depletion.[29]

A case presented by Conn* at the 1954 annual meeting of the Central Society for Clinical Research had clinical features identical with those of the case reported here and presented at the same meeting.[30] The increased urinary salt-retaining activity found in the present case corresponds with that found by Conn in his patient, and the term "primary aldosteronism" appears to be quite appropriate, especially in view of the studies made by Cope[27] in a case probably essentially identical with that of Conn and our case.

Paradoxic sodium diuresis was found by Conn two to three days after administration of either hydrocortisone or adrenocorticotrophic hormone, coincident with increase in excretion of 17-hydroxycorticoids. In the present case intravenous injection of cortisone resulted in a fall in the blood eosinophil count, and an immediate outpouring of urine with a marked rise in urinary concentrations of sodium and chloride and a slight rise of potassium. Such responses suggested opposing effects of the 17-hydroxy corticoids as against the action of the corticosterone-like salt-retaining steroid directly within the renal tubular cells.[31]

Whether or not aberration of magnesium metabolism, demonstrated by this patient, was due to oversecretion of corticosterone-like salt-retaining steroid (presumably aldosterone) cannot be determined; however, the tendency toward fecal as well as renal loss of magnesium suggests the presence of some humoral or hormonal factor operating at both loci. The studies on magnesium metabolism after injection of adrenocorticotrophic hormone have been inconclusive.[32] This may be due to the fact that ACTH appears to have very little effect on the secretion of the specific mineralocorticoid.[33]

SUMMARY

A case of spontaneous hypopotassemia, hypomagnesemia, alkalosis and tetany is presented. Metabolic studies indicated excessive excretion of potassium and magnesium in the urine and stool, and concomitant retention of sodium. Potassium supplements resulted in uptake of potassium and loss of sodium from the cells. Alkalosis was attributed to potassium depletion. Evidence is presented that organic renal disease and polyuria *per se* were probably not the primary causes of potassium loss.

Studies of the urine revealed increased excretion of corticosterone-like steroid by chemical tests and increased salt-retaining corticoid by the bioassay method. The entire picture could be explained by oversecretion of corticosterone-like mineralocorticoid, presumably aldosterone.

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ADDENDUM

On February 28, 1954, the patient was operated upon and the left adrenal gland, containing a cortical tumor, 2.5 cm. in diameter and 6.5 gm. in weight, was removed. The normal portions of the gland appeared atrophic. Microscopic examinations showed an active adrenal cortical tumor tissue, resembling the cells of both zona glomerulosa and zona fasciculata. Bioassay of the tumor extract revealed a salt-retaining factor equivalent to 27 μg. of DOCA per gm. of tissue. Dr. Albert Wettstein, of Basle, Switzerland, graciously analyzed the extract chemically and found 1.4 μg. of aldosterone and 33 μg. of corticosterone per gm. of tumor tissue. Preoperative twenty-four-hour urine contained 16.8 μg. of aldosterone. These values agreed well with the bioassay results.

Subsequent to surgery, the blood pressure and the biochemical abnormalities have become normal, implicating the tumor etiologically.

A tumor was also found in Conn's case.[34]

* See footnote on page 976.

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(ab.) = Abstracts; (CPC) = Clinico-pathologic Conference; (E.) = Editorial

Subject Index

Subject Index

Subject Index

The American Journal of Medicine

Volume XIX
JULY TO DECEMBER
1955

NEW YORK MCMLV
Printed in the United States of America

CONTENTS OF VOLUME XIX
ORIGINAL ARTICLES

Contents

Contents

"Smoothage-Bulk" Restores Normal Peristalsis

The gentle distention of the bowel wall provided by Metamucil® is physiologically corrective in constipation management.

Normal peristaltic movements of the bowel depend on the consistency and quantity of the material within the lumen. In constipation, hypohydration accounts for the hard consistency and inadequate quantity of the fecal mass. With Metamucil, stool quality becomes soft and plastic, while stool quantity is increased to produce gentle distention, the natural stimulus to peristalsis.

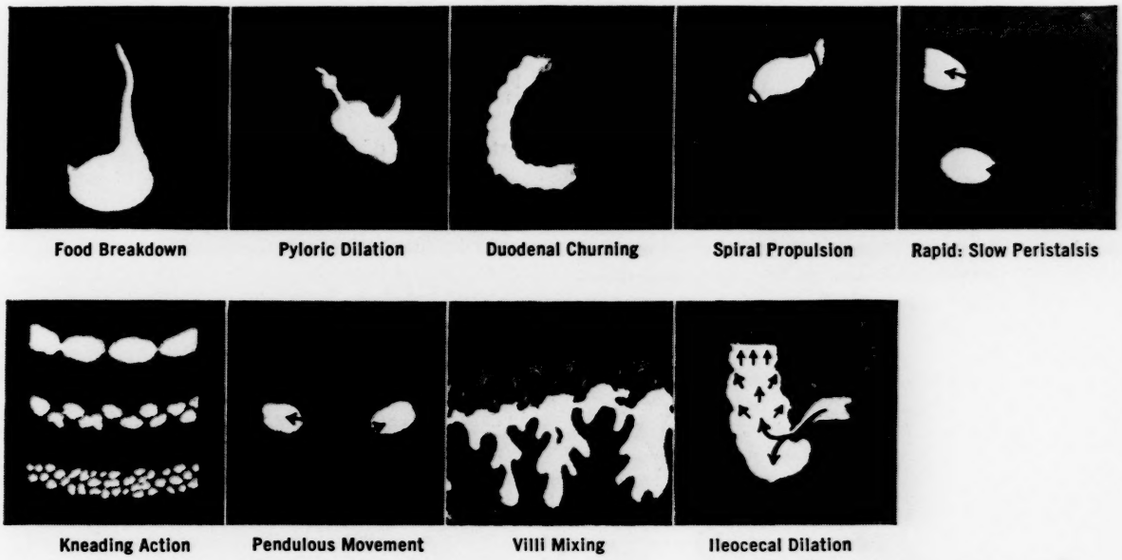
Metamucil is the highly refined mucilloid of the Plantago ovata (50%), a seed of the psyllium group, combined with dextrose (50%) as a dispersing agent.

The usual adult dose is one rounded teaspoonful of Metamucil powder in a glass of cool water, milk or fruit juice one to three times daily. An additional glass of liquid may be taken if indicated.

Metamucil is supplied in containers of 1, ½ and ¼ pound.

G. D. Searle & Co., Research in the Service of Medicine.

TYPES OF MOVEMENT WITHIN THE BOWEL



SEARLE

new...paired piperidol action
for functional gastrointestinal complaints

rapid
visceral eutonic, Dactil®

prolonged
cholinolytic, Piptal®

relief throughout the G. I. tract

Tridal

TRIDAL permits more comprehensive control of gastrointestinal complaints by providing the combined benefits of two piperidols. The local action of Dactil* works immediately to give **rapid** relief of gastrointestinal pain and spasm; the potent cholinolytic Piptal† reinforces relief and provides **prolonged** normalization of secretion and motility.

TRIDAL is singularly free from urinary retention, constipation, dry mouth, blurred vision.

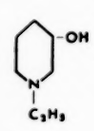
dosage: One TRIDAL Tablet two or three times a day and at bedtime. Unless rapidly swallowed with water, TRIDAL will produce some lingual anesthesia.

Each TRIDAL Tablet contains 50 mg. of Dactil and 5 mg. of Piptal. Bottles of 50 compressed, uncoated tablets.

*Dactil (the ***only*** brand of N-ethyl-3-piperidyl diphenylacetate hydrochloride): the piperidol to prescribe alone when no interference with digestive secretion is desired.

†Piptal (the ***only*** brand of N-ethyl-3-piperidyl-benzilate methobromide): the piperidol to prescribe alone when peptic ulcer is known to be present and normalization of secretion as well as motility is desired.

Lakeside Laboratories, Inc. PIONEERS IN PIPERIDOLS MILWAUKEE 1, WISCONSIN



93155

terminates acute attacks—often in 20 minutes
prevents recurrences—half-strength suppository 2 or 3 times daily

safe—avoids the hazards of parenteral medication

effective—acts even in epinephrine-fast patients

stable—special nonreactive base* avoids deterioration, ensures full therapeutic effect

*melts at body temperature

Supplied: Boxes of 12, full strength—aminophylline 0.5 Gm. (gr. 7½), sodium pentobarbital 0.1 Gm. (gr. 1½). Also available in half strength.

AMES COMPANY, INC • ELKHART, INDIANA

64555

Latest data on effectiveness of Furadantin®

brand of nitrofurantoin, Eaton

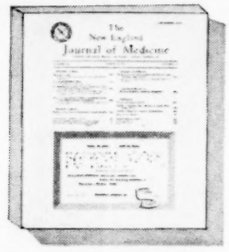
in urinary tract infections

Investigators:

Latest data on effectiveness of Furadantin

Flippin, H. F., and Eisenberg, G. M.: Antimicrobial Therapy in Medical Practice, Philadelphia, F. A. Davis Co., 1955, p. 40.

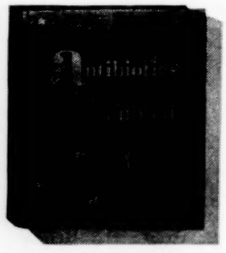
Clinical studies have demonstrated rapid clinical response in cases of cystitis and pyelonephritis, including infections caused by refractory organisms.



Trafton, H. M., et al.: New England J. Med. **252:** 383, 1955.

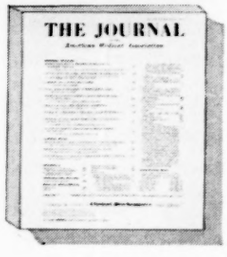
13 acute cases . . . 6 appeared cured . . . 6 markedly improved with no relapses.

36 chronic infections: 30 showed symptomatic improvement, frequently within 24 hours.



Beutner, E. H., et al.: Antibiotics Annual, 1954-1955, New York, Medical Encyclopedia, Inc., 1955, p. 988.

30 chronic urinary tract infections: Of 47 strains of bacteria isolated from these patients, 29 strains (62%) were eradicated by Furadantin.



Hasen, H. B., and Moore, T. D.: J.A.M.A. **155:** 1470, 1954.

Of patients with acute urinary tract infections, 95.7% were benefited. Patients with chronic infections and those with organic or obstructive lesions were benefited in 82% of cases.

Dosage — average adult: four 100 mg. tablets daily, 1 tablet with each meal and 1 tablet on retiring, with food or milk.

Furadantin tablets, 50 and 100 mg. in bottles of 25 and 100. Furadantin Oral Suspension (5 mg. per cc.), bottle of 4 fl.oz. (118 cc.).

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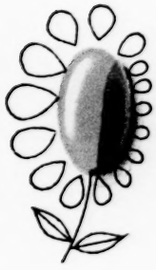
NORWICH • NEW YORK

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS O_2N R PRODUCTS OF EATON RESEARCH

the only

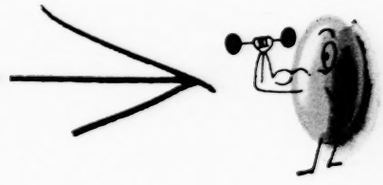
Therapeutic Formula

multivitamin tablet...



THIS SMALL...

THIS POTENT...



Vitamin A	25,000 U.S.P. units (synthetic)
Vitamin D	1000 U.S.P. units (viosterol)
Thiamine Mononitrate	10 mg.
Riboflavin	5 mg.
Nicotinamide	150 mg.
Vitamin B_{12}	6 mcg.
Ascorbic Acid	150 mg.

A solid tablet, no fish-oil taste, odor, burp or allergies.

THIS PLEASING

is OPTIMUM®

(Abbott's Therapeutic Formula Multivitamins) Abbott

502085

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☐ GASTROINTESTINAL PHYSIOLOGY	$2.00
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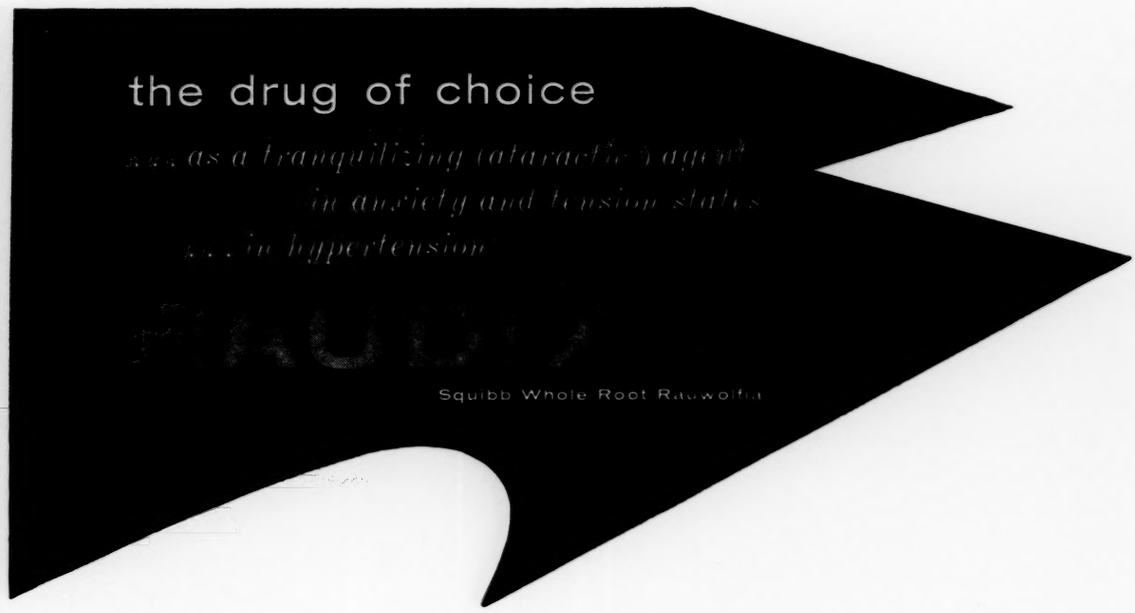


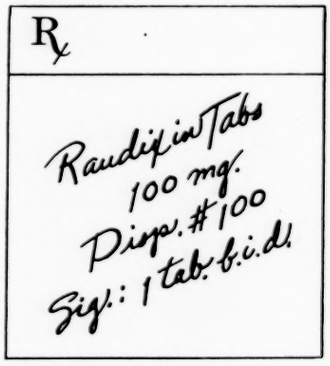
As a tranquilizing agent in office practice, Raudixin produces a calming effect, usually free of lethargy and hangover and without the loss of alertness often associated with barbiturate sedation. It does not significantly lower the blood pressure of normotensive patients.

In hypertension, Raudixin produces a gradual, sustained lowering of blood pressure. In addition, its mild bradycardic effect helps reduce the work load of the heart.

- **Less likely to produce depression**
- **Less likely to produce Parkinson-like symptoms**
- **Causes no liver dysfunction**
- **No serial blood counts necessary during maintenance therapy**

- Raudixin is not habit-forming; the hazard of overdosage is virtually absent. Tolerance and cumulation have not been reported.
- Raudixin supplies the *total* activity of the whole rauwolfia root, accurately standardized by a rigorous series of test methods. The total activity of Raudixin is not accounted for by its reserpine content alone.

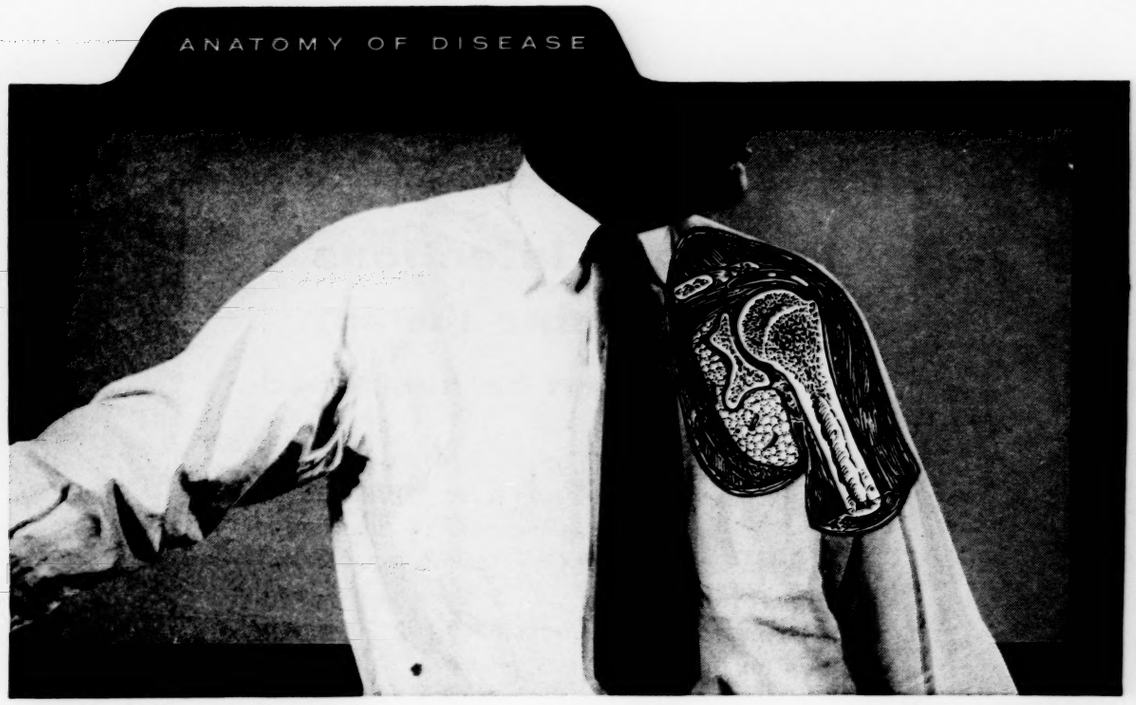
Supply: 50 mg. and 100 mg. tablets, bottles of 100 and 1000.



*Ataractic, from ataraxia: calmness untroubled by mental or emotional excitation. (Use of term suggested by Dr. Howard Fabing at a recent meeting of the American Psychiatric Association.)

SQUIBB

"RAUDIXIN"® IS A SQUIBB TRADEMARK



now . . . *reinforced anti-inflammatory action*

for better results in rheumatic and arthritic conditions

Armyl+F

Armyl + F greatly reinforces the antiarthritic and antirheumatic action of the salicylates. Synergistic action of the combination of agents in Armyl + F produces significantly better patient response with an extremely low dose of corticoid.

Each Armyl + F capsulette contains:

Compound F (hydrocortisone-free alcohol)	2.0 mg.
Potassium Salicylate (5 gr.)	0.30 Gm.
Potassium Para-aminobenzoate (5 gr.)	0.30 Gm.
Ascorbic Acid	50 mg.

Bottles of 50 capsulettes.

but when the salicylates alone are enough

Armyl® for high salicylate blood levels . . . relief of pain . . . antihemorrhagic protection.

Each enteric-coated tablet contains:

Sodium Salicylate (5 gr.)	0.3 Gm.
Sodium Para-aminobenzoate (5 gr.)	0.3 Gm.
Ascorbic Acid (50 mg.)	0.05 Gm.

Bottles of 100. Also available: Armyl with ½ gr. Phenobarbital; Armyl Sodium-Free; Armyl Sodium-Free with ½ gr. Phenobarbital.

THE ARMOUR LABORATORIES

A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

NOW—EFFECTIVE STEROID HORMONE THERAPY OF RHEUMATIC AFFECTIONS WITH GREATER SAFETY AND ECONOMY

PABALATE-HC

Robins

Pabalate with Hydrocortisone

Clinical evidence indicates that, in Pabalate-HC, the synergistic antirheumatoid effects of hydrocortisone, salicylate, para-aminobenzoate, and ascorbic acid achieve satisfactory remission of symptoms in *up to 85% of cases studied*

—with a much higher degree of safety

—even when therapy is maintained for long periods

—at significant economy for the patient

FORMULA

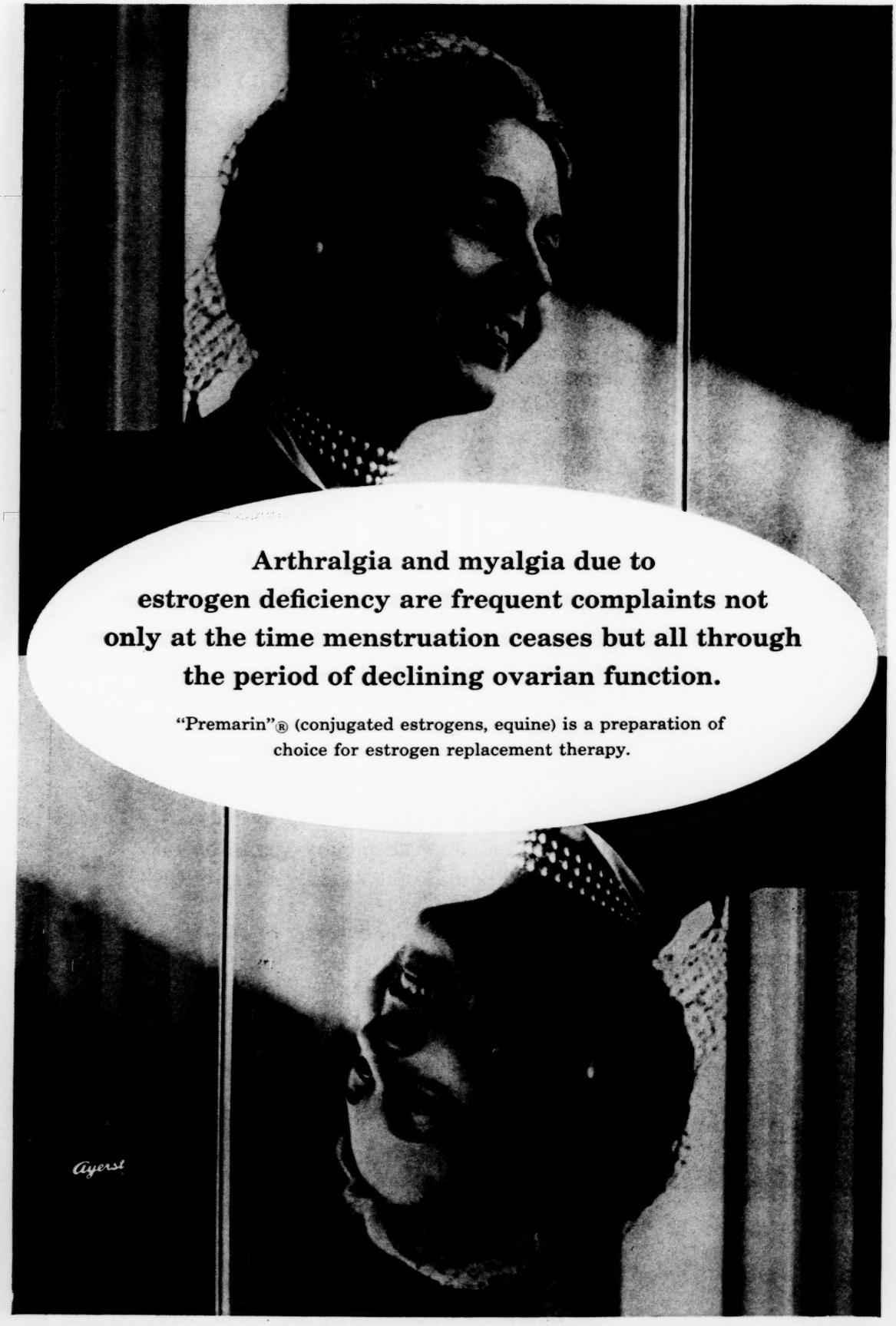
In each tablet:	
Hydrocortisone alcohol	2.5 mg.
Potassium salicylate	0.3 Gm.
Potassium para-aminobenzoate	0.3 Gm.
Ascorbic acid	50.0 mg.

DOSAGE: Two tablets four times daily.
Additional information on request.

Each tablet of Pabalate-HC contains 2.5 mg. of hydrocortisone—50% more potent than cortisone, yet not more toxic.

AVAILABLE FOR YOUR PRESCRIPTION NOW

A. H. ROBINS CO., INC. RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit since 1878


Arthralgia and myalgia due to
estrogen deficiency are frequent complaints not
only at the time menstruation ceases but all through
the period of declining ovarian function.
"Premarin"® (conjugated estrogens, equine) is a preparation of
choice for estrogen replacement therapy.
Ayerst

Tetrazets®

BACITRACIN-TYROTHRICIN-NEOMYCIN-BENZOCAINE TROCHES

in sore-throat weather—a 4-in-1 attack

MAJOR ADVANTAGES: Provide three potent antibiotics
Effective against both gram-positive and

Winds and showers bring sore and inflamed throats; new TETRAZETS provide the ideal topical treatment.

TETRAZETS are soothing, pleasant-tasting troches, each containing bacitracin, tyrothricin and neomycin, with benzocaine, added for its anesthetic effect.

The 3 antibiotics together (1) enhance the antibacterial potency, (2) extend the antibacterial range, and (3) minimize development of secondary invaders.

Prescribe TETRAZETS before and after tonsillectomies, too. They are valuable also as an adjunct to parenteral antibiotic therapy of deep-seated infections such as Vincent's infection.

Supplied: Vials of 12 troches, each troche containing 50 units zinc bacitracin, 1 *mg.* tyrothricin, 5 *mg.* neomycin sulfate with 5 *mg.* benzocaine.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION of MERCK & CO., INC.

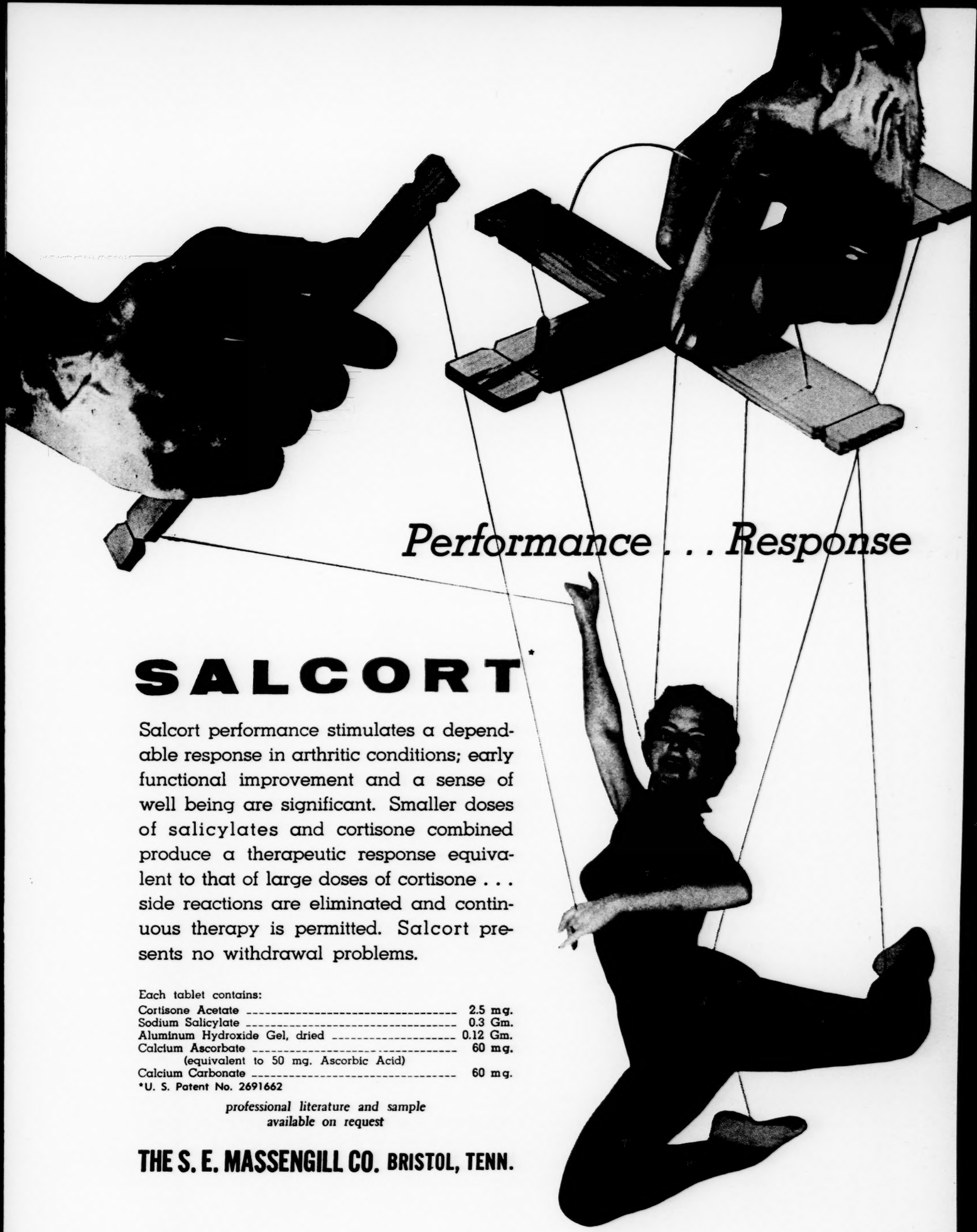
Non-narcotic

cough specific—

Romilar 'Roche' is at least as effective as codeine in relieving cough -- but it does not constipate and is not habit-forming. ~~10~~ mg Romilar® equals 15 mg (1/4 gr) codeine. Romilar is available as a syrup, in tablets and as an expectorant.

More and more physicians —

...are prescribing Gantrisin® 'Roche.' Why? Because they've found that this single, soluble wide-spectrum sulfonamide is usually both effective and well tolerated. There are over 300 references to Gantrisin in recent medical literature.



Performance . . . Response

SALCORT*

Salcort performance stimulates a dependable response in arthritic conditions; early functional improvement and a sense of well being are significant. Smaller doses of salicylates and cortisone combined produce a therapeutic response equivalent to that of large doses of cortisone . . . side reactions are eliminated and continuous therapy is permitted. Salcort presents no withdrawal problems.

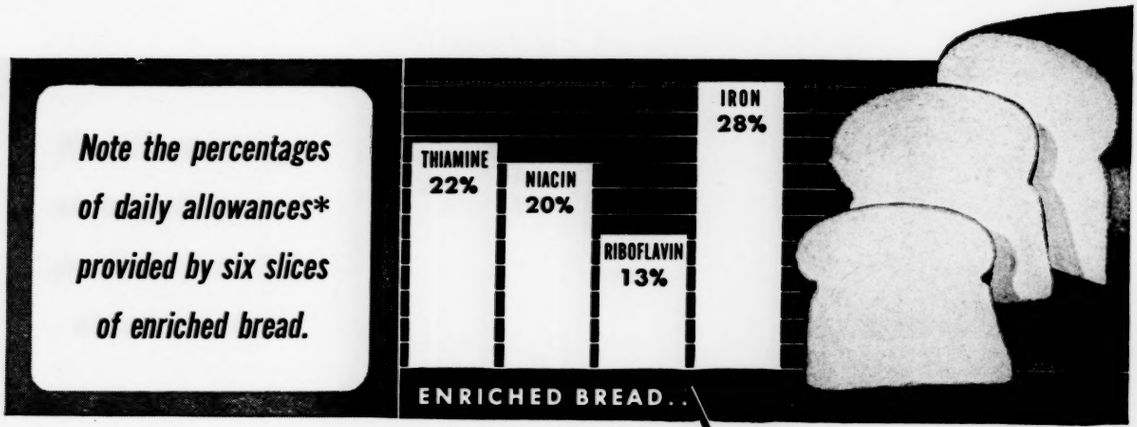
Each tablet contains:

Cortisone Acetate	2.5 mg.
Sodium Salicylate	0.3 Gm.
Aluminum Hydroxide Gel, dried	0.12 Gm.
Calcium Ascorbate (equivalent to 50 mg. Ascorbic Acid)	60 mg.
Calcium Carbonate	60 mg.

*U. S. Patent No. 2691662

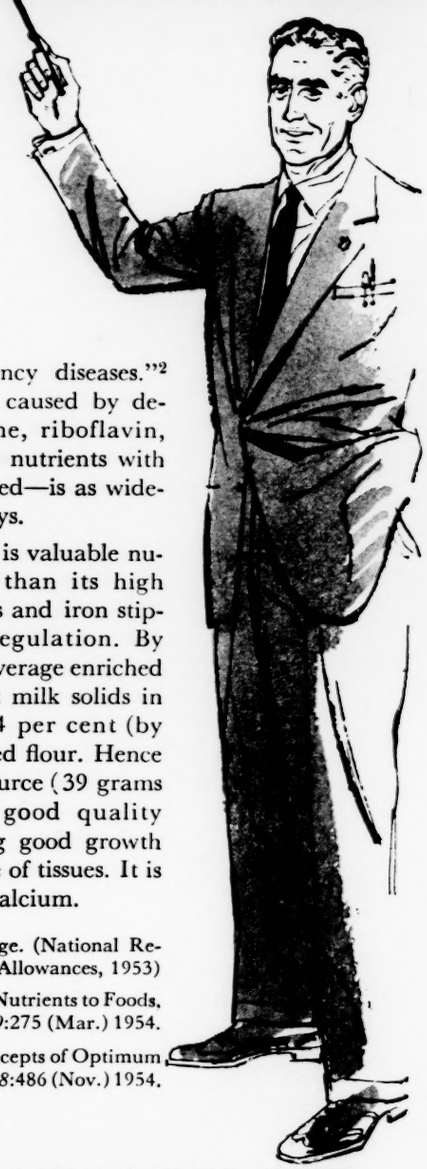
professional literature and sample available on request

THE S. E. MASSENGILL CO. BRISTOL, TENN.



enriched bread

endorsed again by authorities on public health



ENRICHED BREAD, marketed since 1941, recently has been endorsed again by the Food and Nutrition Board of the National Research Council and by the Council on Foods and Nutrition of the American Medical Association.[1] This reaffirmation of endorsement in former years (1939, 1941, 1946) is based on "good evidence" that enriched bread has been "beneficial to the public," has "encouraged sound nutritional practices," and has contributed notably to "correcting deficiencies in the diets of the general population."

Nationally marketed enriched bread merits a large share of the credit for "the great gain in public health" in recent years, attributed to modern food commodities possessing high nutrient content. "Within the past two decades, for the first time in our history we have reached a national pattern of food practices that permits almost a complete escape from the classical forms of nutritional deficiency diseases."[2] None of the diseases caused by deficiencies of thiamine, riboflavin, niacin, and iron—the nutrients with which bread is enriched—is as widespread as in former days.

But enriched bread is valuable nutritionally for more than its high amounts of B vitamins and iron stipulated by official regulation. By commercial practice, average enriched bread contains nonfat milk solids in amounts averaging 4 per cent (by weight) of its contained flour. Hence it also represents a source (39 grams per pound loaf) of good quality protein for supporting good growth as well as maintenance of tissues. It is also a good source of calcium.

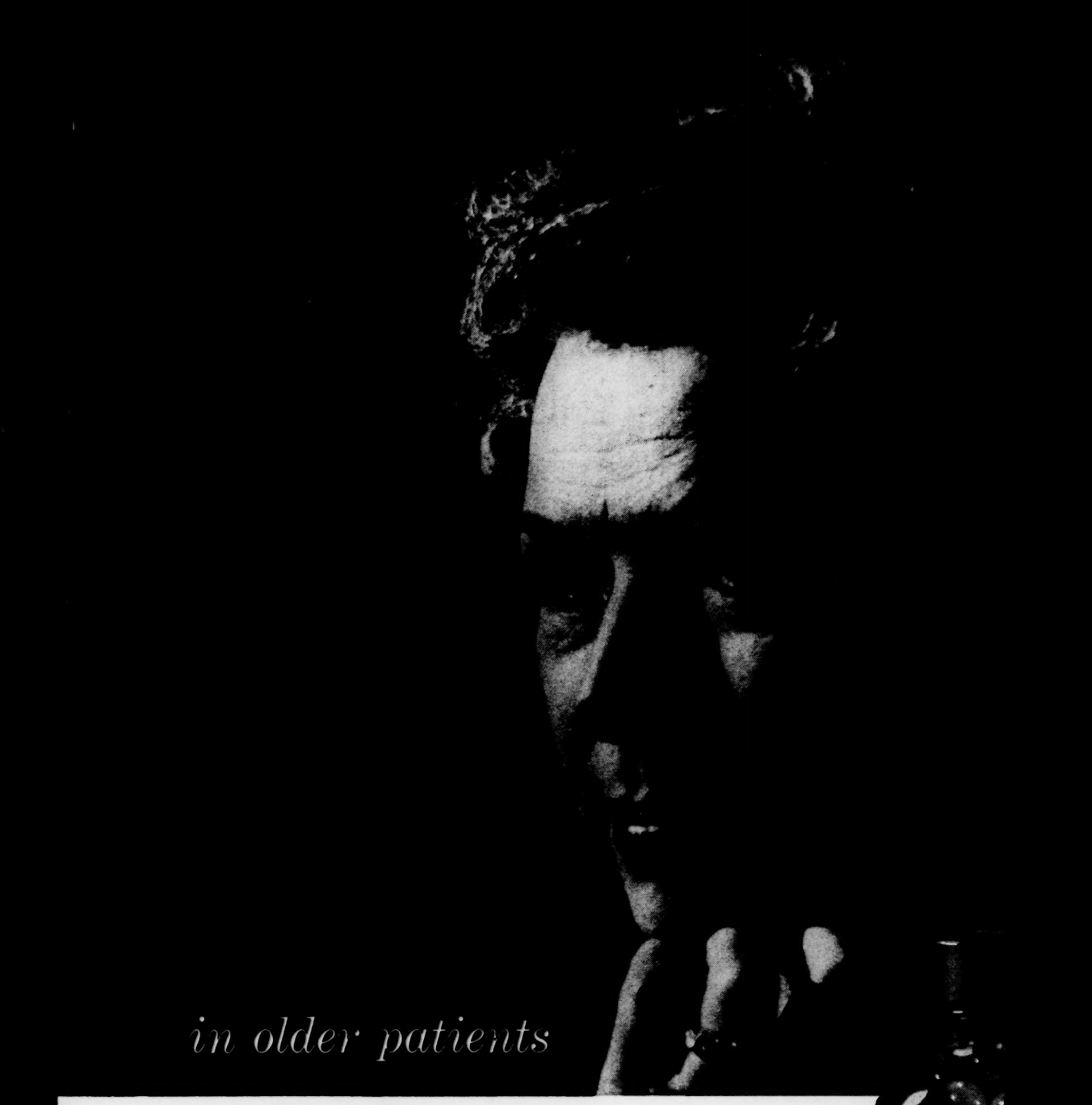
*For man 45 years of age. (National Research Council Dietary Allowances, 1953)

1. The Addition of Specific Nutrients to Foods, Public Health Reports *69*:275 (Mar.) 1954.

2. King, C. G.: Newer Concepts of Optimum Nutrition, Food Technol. *8*:486 (Nov.) 1954.

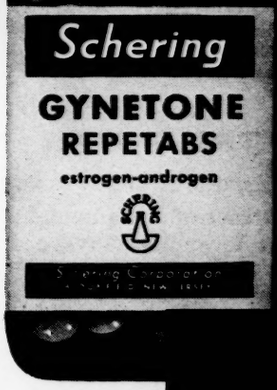
The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE, CHICAGO 6, ILL.



in older patients

rebuild bone—avoid pain, debility, fractures



- promote reconstruction of bone matrix
- stimulate osteoblastic activity
- enhance calcium and phosphorus redeposition

valuable, too, in osteoporosis of menopause, postmenopause, arthritis and long-term ACTH, cortisone, and hydrocortisone therapy.

for individualized therapy: two strengths

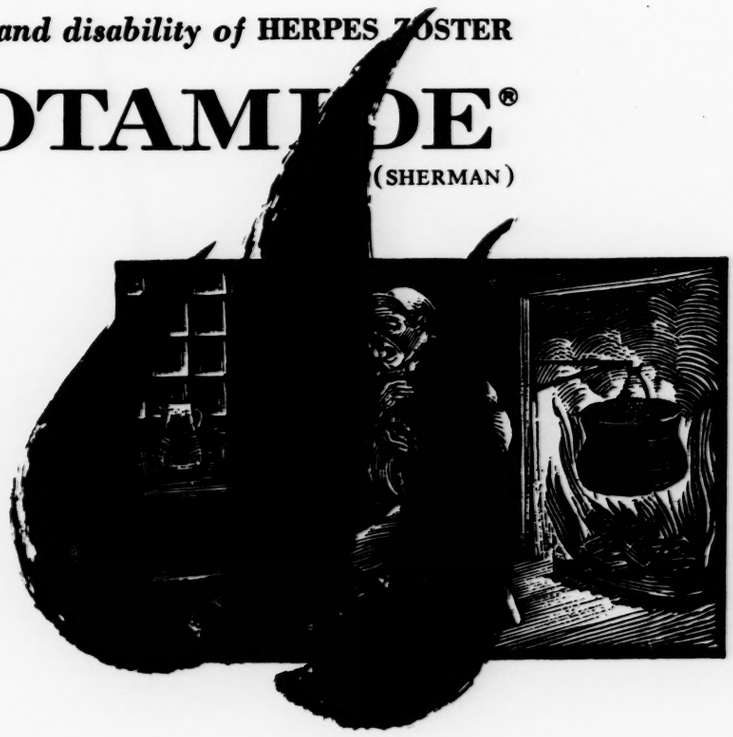
GYNETONE® REPETABS® ".02": ethinyl estradiol 0.02 mg. plus 5 mg. Methyltestosterone U.S.P.

GYNETONE REPETABS ".04": ethinyl estradiol 0.04 mg. plus 10 mg. Methyltestosterone U.S.P.

for the pain and disability of **HERPES ZOSTER**

PROTAMIDE®

(SHERMAN)



published studies show:*

Improvement is "almost immediate," with "good to excellent results" in four out of five patients, and no postherpetic neuralgia in any patient who responded favorably.

Protamide is a sterile colloidal solution prepared from animal gastric mucosa . . . denatured to eliminate protein reaction . . . completely safe and virtually painless by intramuscular injection.

Clinical data on request.

use* PROTAMIDE® *first

in herpes zoster and post-infection neuritis

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS

*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.

ABDEC® DROPS

MEDICAMENTA VERA

Pork in the Dietary During Pregnancy and Lactation

CERTAIN NUTRIENTS are required in greater than normal amounts during pregnancy and lactation. Pork meat, though its cost is low, supplies a remarkably high quantity of the nutrients required by the maternal organism in these periods of physiologic need.

During pregnancy the maternal organism may store 3.3 to 5.5 pounds of protein in excess of that contributed to fetal tissue.[1] Enough iron is stored to approximate the entire amount secreted in the milk during 9 months of lactation, in addition to the iron supplied to the fetus.[2]

The body of the newborn infant contains approximately 500 grams of protein, 14 grams of phosphorus, and 0.5 gram of iron.[3] It is estimated that the lactating mother, through breast milk, provides a 26 week old infant with about 12 grams of protein, 76 grams of lactose, and 1.2 mg. of iron each day.[2]

Pork meat, an excellent source of high quality protein, thiamine, niacin, and iron,[4] also supplies valuable amounts of other B vitamins, as well as phosphorus, magnesium, and potassium. The thiamine content of pork is particularly important, since there are few more valuable food sources of this vitamin.[4]

Pork and pork sausage—economical, good tasting—are valuable components of the dietary of the pregnant or lactating woman. Just how valuable, is shown in the table below.

1. Toverud, K.U.; Stearns, G., and Macy, I.G.: Maternal Nutrition and Child Health, an Interpretative Review, Washington, D.C., National Research Council, Bull. 123, 1950.

2. McLester, J.S., and Darby, W.J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W.B. Saunders Company, 1952, p. 241.

3. Marrack, J.R.: Food and Planning, London, Victor Gollancz, Ltd., 1943, p. 67.

4. Wolgamot, I.H., and Fincher, L.J.: Pork Facts for Consumer Education, Washington, D.C., United States Department of Agriculture, AIB No. 109, 1954.

5. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, Washington, D.C., United States Department of Agriculture, Agricultural Handbook No. 8, 1950.

6. Bowes, A. deP., and Church, C.F.: Food Values of Portions Commonly Used, ed. 7, Philadelphia, Anna dePlanter Bowes, 1951.

Percentages of Recommended Daily Dietary Allowances* for Pregnant (3rd Trimester) and Lactating Women Provided by 3-Ounce Portions of Cooked Pork Meats and Pork Sausage

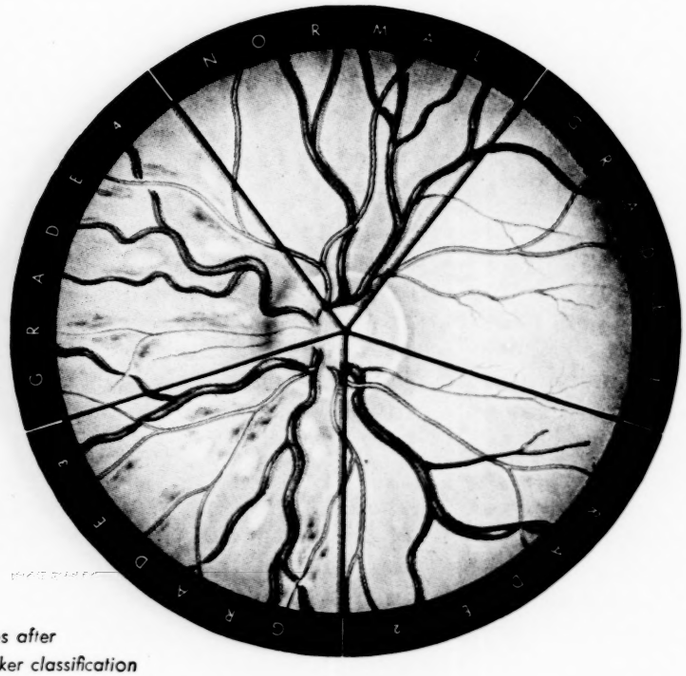
	Protein	Iron	Phosphorus	Thiamine	Riboflavin	Niacin	Calories
PREGNANCY (3rd trimester)							
Ham, without bone, 3 oz., cooked[5]	25.0%	17.3%	13.5%	30.0%	10.0%	26.7%	12.5%
Pork Chops, without bone, 3 oz., cooked[5]	25.0%	17.3%	13.3%	47.3%	10.0%	28.7%	10.5%
Pork Sausage, 3 oz., cooked[6]	17.3%	14.0%	9.2%	27.7%	10.1%	18.5%	14.7%
LACTATION							
Ham, without bone, 3 oz., cooked[5]	20.0%	17.3%	10.1%	30.0%	8.0%	26.7%	10.2%
Pork Chops, without bone, 3 oz., cooked[5]	20.0%	17.3%	10.0%	47.3%	8.0%	28.7%	8.6%
Pork Sausage, 3 oz., cooked[6]	13.8%	14.0%	6.9%	27.7%	8.1%	18.5%	12.0%

*Recommended Dietary Allowances, Washington, D. C., National Academy of Sciences—National Research Council, Publication 302, 1953

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago... Members Throughout the United States



Eye ground changes after
Keith-Wagener-Barker classification

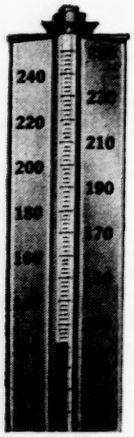
In hypertension, effective reduction of blood pressure is assured in 90% of appropriate cases when dosage is fitted to the requirements of the individual patient. Response is reliable, uniform, prolonged. By-effects are minimal. Convenient t.i.d. oral tablet medication.

There is usually regression in retinal vascular changes, resorption of exudates, subsidence of papilledema, and improvement in vision.

Supplied in scored tablets of 20, 40, and 100 mg., bottles of 100. Also available: Injection, 10 mg. per cc., vials of 10 cc.

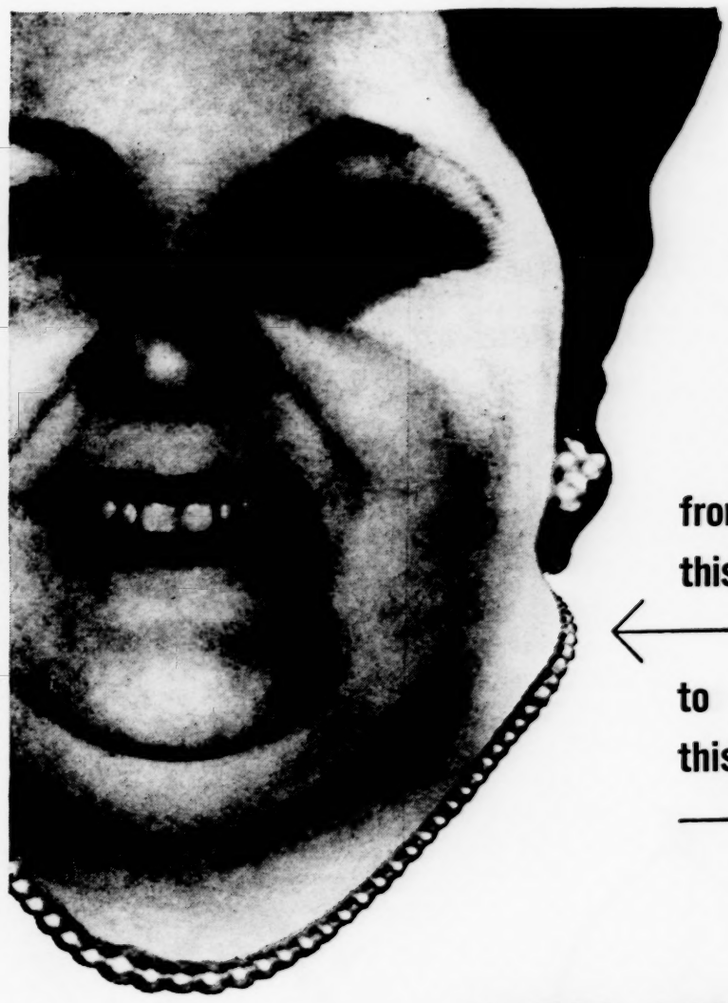
ANSOLYSEN®

TARTRATE (Pentolinium Tartrate)



ALWAYS LOWERS BLOOD PRESSURE

Wyeth®
Philadelphia 2, Pa



from this

to this

safely

with **AM PLUS®**

(dextro-amphetamine plus minerals and vitamins, Roerig)

each AM-PLUS capsule contains:

Dextro Amphetamine Sulfate U.S.P.	5 mg.
Vitamin A (Palmitate)	5,000 U.S.P. Units
Vitamin D (Irradiated Ergosterol)	400 U.S.P. Units
Thiamine HCl U.S.P.	2 mg.
Riboflavin U.S.P.	2 mg.
Pyridoxine HCl U.S.P.	0.5 mg.
Niacinamide U.S.P.	20 mg.
Ascorbic Acid U.S.P.	37.5 mg.
Calcium Pantothenate	3 mg.
Calcium (from Dicalcium Phosphate)	242 mg.
Cobalt (from Cobaltous Sulfate)	0.1 mg.
Copper (from Cupric Sulfate)	1 mg.
Iodine (from Potassium Iodide)	0.15 mg.
Iron (from Ferrous Sulfate)	3.33 mg.
Manganese (from Manganous Sulfate)	0.33 mg.
Molybdenum (from Sodium Molybdate)	0.2 mg.
Magnesium (from Magnesium Sulfate)	2 mg.
Phosphorus (from Dicalcium Phosphate)	187 mg.
Potassium (from Potassium Sulfate)	1.7 mg.
Zinc (from Zinc Sulfate)	0.4 mg.

dosage: Two or three capsules daily, one-half hour before meals.

In bottles of 100 soft, soluble capsules.

1. MacBryde, C. M.: in Current Therapy, W. B. Saunders Co., Philadelphia, 1953, p. 350.

Adequate minerals and vitamins must be supplied in any long-continued weight reducing program.[1]

AM-PLUS: Supplies 11 important minerals and 8 essential vitamins **and** decreases appetite and elevates mood—safely—with dextro-amphetamine.

ROERIG **Chicago 11, Illinois**

EMULSION OF

Mephyton®

(VITAMIN K_1, MERCK)

Preferred product for rapidly normalizing prothrombin levels in the newborn

In fast-moving deliveries, improved prophylaxis against hemorrhagic disease of the newborn is assured by MEPHYTON. The action of this new emulsion of vitamin K_1 is *more rapid, more complete,* and *more prolonged* than that achieved with any of the vitamin K analogues previously considered specific for the control of physiologic hypoprothrombinemia in the newborn. MEPHYTON may be administered prophylactically to the mother or therapeutically to the infant.

INDICATIONS: Hypoprothrombinemia due to antibiotics, salicylates, obstructive jaundice, hepatic disease, impaired gastrointestinal absorption, and anticoagulants such as Dicumarol®, Cumopyran®, Hedulin®, and Tromexan®.

SUPPLIED: In boxes of six 1-cc. ampuls, each cc. containing 50 mg. of vitamin K_1 for intravenous injection.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

Syrup and oral tablets. Each teaspoonful or tablet of **HYCODAN** contains 5 mg. dihydrocodeinone bitartrate and 1.5 mg. Mesopin.* May be habit-forming. Average adult dose, 1 teaspoonful or 1 tablet after meals and at bedtime.

Hycodan®

(Dihydrocodeinone with Homatropine Methylbromide)

*Homatropine methylbromide

BETTER THAN CODEINE FOR COUGH[1]

FASTER
•
LONGER-LASTING
•
MORE THOROUGH

BETTER THAN CODEINE *PLUS* APC FOR PAIN[2]

Percodan®†

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC)

Scored, yellow oral tablets. May be habit-forming. Average adult dose, 1 tablet q. 6 h.

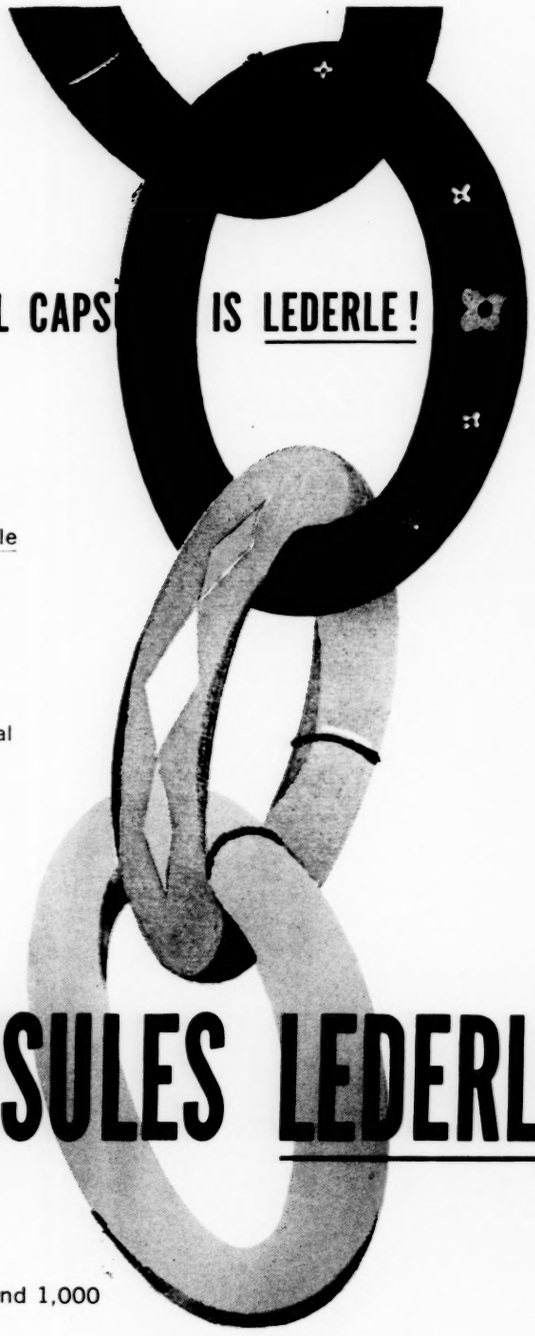
1. Hyman, S., and Rosenblum, S. H.: Illinois M. J. 104:257, 1953.
2. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.

†U. S. Pat. 2,628,185

Literature? write

ENDO PRODUCTS INC., RICHMOND HILL 18, NEW YORK

NOW...
Federal law permits oral prescription



THE LAST WORD IN PRENATAL CAPS[illegible] IS LEDERLE!

PRENATAL CAPSULES Lederle provide the extra vitamins and minerals needed during pregnancy and lactation. Depending on the patient's diet, one to three of these dry-filled capsules is the usual daily dose. But specify that important last word to make certain your patient gets the genuine Lederle formula!

PRENATAL CAPSULES LEDERLE

Packaged in bottles of 100 and 1,000

Each capsule contains:

Vitamin A	2000 U.S.P. Units
Vitamin D	400 U.S.P. Units
Thiamine Mononitrate (B_1)	2 mg.
Riboflavin (B_2)	2 mg.
Niacinamide	7 mg.
Vitamin B_{12}	1 mcgm.
Vitamin K (Menadione)	0.5 mg.
Ascorbic Acid (C)	35 mg.
Folic Acid	1 mg.
Calcium (in $CaHPO_4$)	250 mg.
Phosphorus (in $CaHPO_4$)	190 mg.
Dicalcium Phosphate Anhydrous ($CaHPO_4$)	869 mg.
Iron (in $FeSO_4$)	6 mg.
Ferrous Sulfate Exsiccated	20 mg.
Manganese (in $MnSO_4$)	0.12 mg.

Lederle LEDERLE LABORATORIES DIVISION *AMERICAN Cyanamid COMPANY* Pearl River, New York

THIS IS

Rauwiloid®

The original alseroxylon fraction of India-grown Rauwolfia serpentina, Benth.

All the hypotensive alkaloids of Rauwolfia—not merely a single isolated substance

Free from the dross of the whole root
Gently antihypertensive
Tranquilizing
Bradycrotic
Free from undesirable side actions
Single daily dose

DOSAGE: Merely two 2 mg. tablets at bedtime. After full effect 1 tablet usually suffices. Available in bottles of 60, an average month's supply.

FIRST THOUGHT IN HYPERTENSION

Riker

LOS ANGELES

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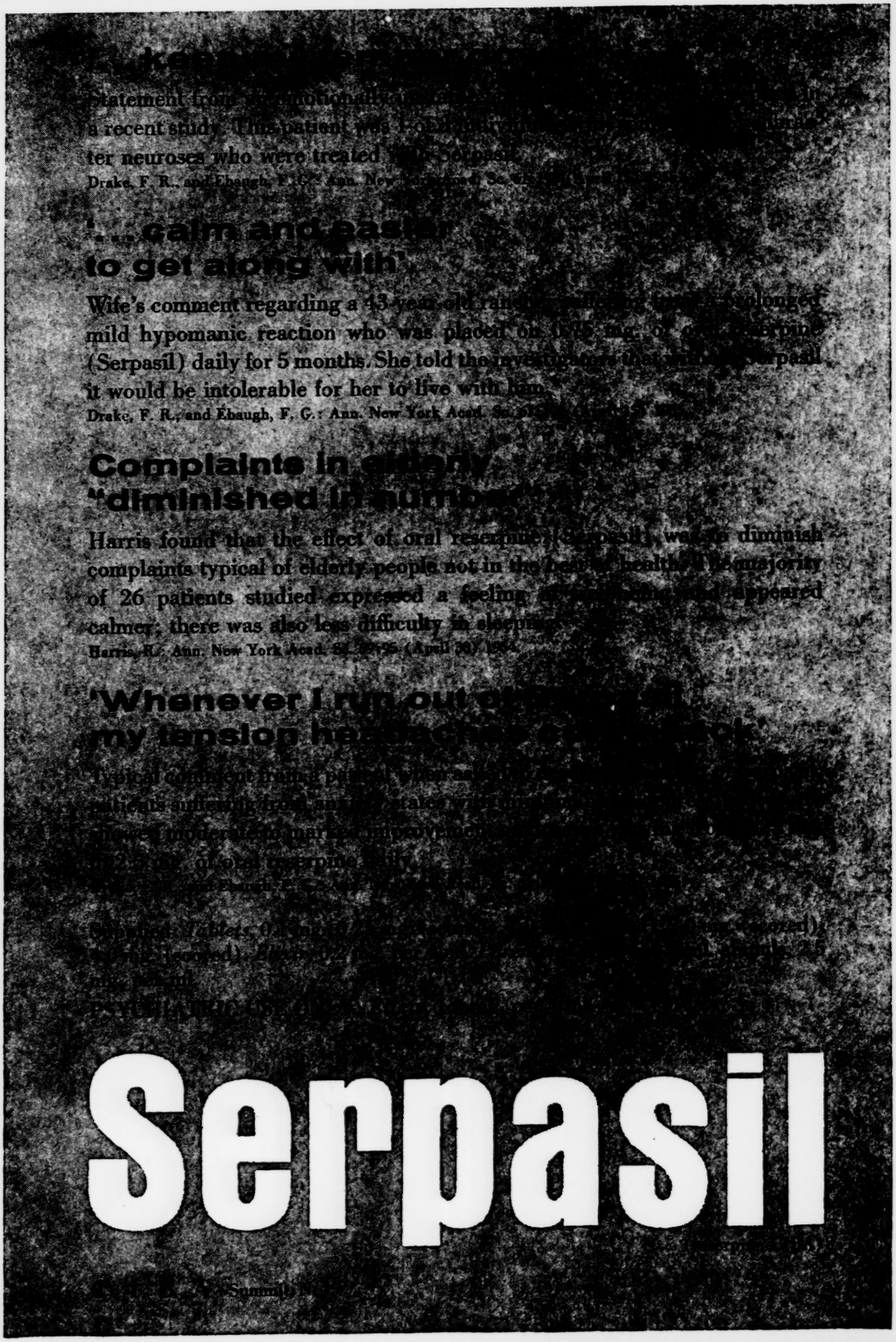
December, 1955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